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PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

64TH MEETING

ISSUE:

GUIDANCE DOCUMENTS ON DEVELOPING ANTIMICROBIAL DRUGS

GENERAL CONSIDERATIONS AND INDIVIDUAL INDICATIONS

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P R O C E E D I N G S

Opening Remarks

DR. CRAIG: Good morning to everyone. We will get started. My opening remarks are very brief. They are essentially to welcome you and to let you know that we will try and get done by 1 o'clock at the latest, hopefully around 12:00. I would encourage all of the speakers this morning to try and stay within the allotted time.

Again, just for the sake of the record, we need to go around the table here and announce everybody that is here.

Do you want to start, Dr. Murphy?

DR. MURPHY: This looks like the survivors group here. Dianne Murphy, Office Director, ODE 4.

DR. CHIKAMI: Gary Chikami, Director, Division of Anti-infective Drug Products.

DR. ALBRECHT: Renata Albrecht, Deputy Director, Division of Special Pathogens and Immunologic Drug Products.

DR. RELLER: Barth Reller, Duke University.

MS. McGOODWIN: Ermona McGoodwin, FDA.

DR. CRAIG: Bill Craig, University of Wisconsin.

DR. NORDEN: Carl Norden, University of New Jersey, Cooper Hospital.

DR. CHRISTIE: I am Celia Christie, University of

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DR. HENRY: Nancy Henry, Mayo Clinic.

DR. RODVOLD: Keith Rodvold, University of Illinois at Chicago.

DR. SOPER: David Soper, Medical University of South Carolina at Charleston.

DR. CHESNEY: Joan Chesney, University of Tennessee in Memphis.

DR. CRAIG: The first topic this morning--in fact, we are going to go through several topics, toxicology, microbiology, clinical pharmacology, before we come up to our last disease entity to discuss.

The first one is going to be a toxicology update and the FDA presentation will be given by Dr. Osterberg.

Toxicology Update

FDA Presentation

DR. OSTERBERG: Good morning.

[Slide.]

What I would like to do this morning is briefly go through the pharm-tox section of the guidance document and, following that, address three questions and comments that we received in response from the public.

[Slide.]

The first issue is the use of the preclinical

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pharm-tox data. The first one would be to identify target organs and tissues. This would be for monitoring during the clinical trials and also for inclusion in the investigator's brochure.

There is also a need to identify specialized safety problems for monitoring during the clinical trials like what the fluoroquinolones produce, Q-Tc prolongation, and also to identify the toxicological profile which is the complete spectrum of toxicities that the drug is capable of producing in the animals so that some comparison later on can be made with the human toxicities that may emerge.

Also, we use this data to select the starting doses for the initial clinical trials and, perhaps, some of the future clinical trials but definitely for the repeat-dose animal toxicology studies.

[Slide.]

The types of toxicity studies that we look at in the pharm-tox arena are the acute and multiple-dose who are subchronic studies. We look at the chronic studies which are six months or greater. We look at the two-year bioassays for carcinogenicity. At least right now, we look at two years. We are looking on shortening those tests with specific innovations.

We look at genetic toxicology, both in vivo and in

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vitro, and this, of course, constitutes mutagenicity and clastogenicity effects on chromosomes. We look at reproductive toxicology, specifically segments 1, 2 and 3, which is impairment of fertility, teratology and prenatal and postnatal toxicities.

We look for specialized studies on occasion. Inhalation; we have look ed at tobramycin for inhalation which, for antibiotics, is sort of rare. We looked at phototoxicity and photocarcinogenicity for the fluoroquinolones which have this potential in animals and, of course, phototoxicity in humans.

We look also for arthropathy which we know the fluoroquinolones in juvenile animals have the ability to produce and, also, in the human, we know that it causes tendon rupture on occasion. We look at allergenicity on occasion for beta lactam antibiotics.

[Slide.]

Other studies that we utilize are safety pharmacology studies which allows the drug to be tested in various systems and in various reflexes, et cetera, to get a better perspective on what the compound is able to do in a the pharmacologic sense but, also, it gives us some signals as to what types of special toxicology concerns we may have.

In some cases, as you know, the fluoroquinolones

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produce convulsions and, therefore, when we see this in certain types of safety pharmacology studies, we can ask specific questions and design studies to see that.

We look for absorption, distribution, metabolism, excretion which, of course, is pharmacokinetics and, at the higher end of the dose-response curve, we look for toxicokinetics.

[Slide.]

The purpose of the animal-toxicity studies are to identify potential human toxicities to alert the clinician to potential problems during clinical trials. We also use this information to design special specific animal tests to further define the toxicity or its mechanism. Again, the convulsant activity of some of the fluoroquinolones in the animal models are an example.

We also like to suggest specific toxicities to be monitored during the clinical trials, which I have mentioned, such as hearing loss that we see with the aminoglycosides, neurotoxicity, again, that we see with some of the fluoroquinolones and well as Q-Tc prolongation and allergenicity.

[Slide.]

We also like to investigate in the animals toxicities that are unethical to examine in humans.

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Obviously, carcinogenicity and mutagenicity, clastogenicity or genetic toxicology, teratology, reproductive toxicity and, of course, overdosage. In these categories, of course, you see information in the product labeling.

We also like to see the toxicity profile in the animals because it is unethical to do these types of tests in humans. Of course, we don't want to see extensive toxicity and we certainly don't want to see mortality.

[Slide.]

I will start to address the public questions and comments that we received. The first question that we received was should sponsors plan to complete juvenile animal studies prior to proposing to initiate single and multiple-dose clinical studies in pediatric patients.

[Slide.]

The answer is on a case-by-case basis, yes, because usually we know about the class of drugs and can make extrapolations to juveniles based upon pharmacokinetic data, body-surface area comparisons, use the rule of Clark, et cetera, to help us make these dose selections. If we know about the class of compounds, we are pretty confident in the toxicity and what it may do in juveniles.

But, for new and unique chemical classes, we may request juvenile studies. If we have never seen the

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chemical before in a unique class, then we should ask for a lot of studies in juvenile animals to see what it may do in an immature enzyme systems, et cetera.

We also suspect adverse reproduction effects if we see it in the animal model which utilizes, of course, the juvenile or the young-adult animals, things like testicular toxicity. We of course, are concerned for the juvenile because of maturation arrest.

One of our concerns is irreversibility, so we would ask for studies to measure whether or not testicular atrophy was reversible in the juvenile animals. We also suspect juvenile susceptibility on occasion; arthropathy with the fluoroquinolones, ototoxicity, of course, with the immunoglycosides, and immature blood-brain barriers.

This would ask us to, perhaps, request a juvenile toxicity study.

[Slide.]

The second question is does the Division of Anti-Infective Drug Products currently accept the ICH guidelines on the topics of reproductive toxicology and mutagenicity or should sponsors rely specifically on the FDA guidelines.

[Slide.]

I thought I would mention just what is the ICH at

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this point for those of you who may not be familiar with it. The ICH is really an international conference on harmonization of technical requirements for registration of pharmaceuticals for human use. Now you know why we call it the ICH. Its purpose is to increase drug development among three major drug development regions of the world, specifically the United States, Japan and Europe, by reducing duplication of efforts, thus saving time in the development and approval of drugs.

It also harmonizes and updates technical requirements, requests early exchanges of data and meetings on emergent issues to address situations before they become problems.

[Slide.]

With response to whether or not we use ICH guidelines or the FDA guidelines, CDER has had historical toxicity guidelines but they are fairly old and they are not up to date. Therefore, over the years, we have used the Center for Food Safety and Applied Nutrition's reproductive toxicity guidelines in the Red Book and the Center for Veterinary Medicine's genetic toxicity section and its threshold assessment guideline.

These are somewhat up to date and are being improved right now. However, the Center for Drugs is a

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signatory to the ICH. It has helped to write the safety guidances and, therefore, it is expected to implement them. So when the expert working group on a particular guideline and the steering committee, which is the governing body of the ICH, finally signs off on the step-4 document and the document is published in the Federal Register in this country, and the similar documents in the other two regions at step 5.

Everybody is expected as signatories to implement them.

[Slide.]

The last comment that we received from the public is that preclinical toxicity tests should identify the complete spectrum of toxicities of a drug in animals. Interspecies differences in pharmacologic properties of the drug give rise to toxicities in humans that are not seen in animals.

Adjunctively, one may see toxicities in animals that are not seen in humans. This is true. However, CDER recognizes that differences in pharmacokinetics and enzymes in receptive populations, et cetera, can account for toxicities seen in humans but not seen in animals and vice versa. So we agree with the statement.

Furthermore, ethical reasons will not allow higher

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drug doses to be given to humans to produce the complete spectrum of toxicity in humans. This is unethical, as we discussed before. Therefore, CDER requires sponsors to do what they can do to provide useful safety data as long as there is good common sense and good science involved in it.

Thank you for your attention.

DR. CRAIG: Any comments, questions, on the material that was presented?

If not, thank you very much.

We will move on to the next topic which is microbiology and the FDA presentation will be given by Sousan Altaie.

Microbiology Update

FDA Presentation

DR. ALTAIE: Good morning.

[Slide.]

This morning, I am going to try to answer all the questions that were given to us by industry and that we were not able to incorporate in the individual indications. Most of my comments have been incorporated with their answers in the individual indications and you have been listening to them for the past two days.

These are the remaining issues that could not fit within the indications and I am addressing them separately.

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[Slide.]

The question from industry was raised about the certification and qualification of the labs and what kind of certification for the outside-the-United-States laboratories is accepted.

[Slide.]

We do recognize that, outside the United States, there are several bodies of regulatory agencies and we don't know what kind of regulations they have or the standardization or how they compare to each other across the continent.

So we recognize this fact and we just say that if you use an outside laboratory to, at least, submit the quality-control/quality-assurance programs and their protocols in as much detail as you can for us to be able to validate their results that come out of these laboratories.

[Slide.]

There was another comment independently and it encouraged the division or the FDA to cooperate with NCCLS and to prevent disparities in setting breakpoints and quality-control ranges for susceptibility testing.

[Slide.]

In fact, the two divisions, at least that I know of, the Division of Anti-Infective Drug Products and the

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Division of Special Pathogens and Immunological Drugs members do have a presence in NCCLS committees as observers, as voting members and as consultants. Members of the Division of Anti-Infective Drug Products do attend the semi-annual meetings where these breakpoints for quality control and the drugs are set.

So we do have an appearance and we are doing the best we can in trying to collaborate with NCCLS on these disparities.

[Slide.]

There is another comment referring to HCFA licensure being not required in the U.S. for the laboratories to be able to operate. And that would prevent the College of American Pathology Certified labs to be included in the laboratories that are accepted by the FDA.

I have good news and bad news. I will give you the good news first. CAP has obtained a deemed status and now is accepted by HCFA to certify laboratories.

[Slide.]

The bad news is, unfortunately, it is in the law that the laboratories who test human specimens must be certified under CLIA '88. There are few exceptions. That is the VA hospital and the NIDA which is the National Institute on Drug Abuse that are exempt. Also, the research

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labs are exempt and the forensic labs are exempt.

For the NIDA only the section that does the drug testing is exempt, not the rest of the laboratory. So you still need to be under CLIA certification before using a laboratory as a qualified lab.

[Slide.]

I need to give you a little bit of background before I go into the next comment. The background is this; in the general document guidelines, under the microbiology issue and in the study design section, we address the antimicrobial susceptibility testing and that the patient isolates should be stored until the clinical outcome is known so that isolates from patients who failed can be studied further.

We also state in the same paragraph that it may be appropriate for a systematic prospective sample of all strains to be retested by the sponsor or by a reference laboratory just to do a spot check on the results and the comment.

[Slide.]

So the comment came from industry saying that such retesting gives value only in limited situations. For example, they list the non-U.S. laboratories where the testing was done on the site abroad. They state, however,

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that routine testing, even if for a prospective sample, is an unnecessary expense.

[Slide.]

Our response to that is that we recognize that and we reworded the document to read as follows: "If the antimicrobial susceptibility testing is performed in a non-U.S. laboratory, it may be appropriate for a random sample of clinical strains to be retested by the sponsor in order to assure the validity of the antimicrobial susceptibility test results."

This statement currently does not exist in the document you have in your hand, but it will make its way into the document before it is published.

[Slide.]

The next question from industry was in regards to dilution testing. This particular quotation was taken out of the document, "What do you mean by full range of dilution? Does this mean clear endpoints?"

[Slide.]

The actual statement in the document does state that yes, we need clear endpoints. And the statement reads as follows: "A full range of dilution should be tested to yield on-scale rather than off-scale endpoints," which means clear endpoints.

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[Slide.]

Background. Before we go into another question, I need to give you a little bit more background. To be evaluable for microbiological assessment, the pathogen should be susceptible to the study and control drugs." This is the result of the way we write the labels. In the labels, we say the drug is working against susceptible strains of such-and-such organism in such-and-such indication.

That statement is correct because we label the drugs that way.

[Slide.]

The comment from industry came, "This situation really does not allow for complete evaluation of the drug which will be used empirically for treatment of all pathogens, not just the susceptible ones." And the suggestion was made that the pathogen susceptibility requirements for evaluability be deleted from all indications.

[Slide.]

It is easier said than done. There is an ethical issue with that; how can an investigator be asked to keep a patient on study knowing that the cultured isolate is resistant to the study or the control drug. It may be okay

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in an UTI but it won't be ethical in a meningitis study.

[Slide.]

Despite that, we realize the value of including all patients if they are doing well. So we are trying to put the following or a variation of this following statement in all indications which says, "If the patient is judged by the investigator to be responding well clinically to the therapy, then the patient may be kept in the study and counted evaluable if they meet all the other evaluability criteria."

Actually, as a microbiologist, I am pretty pleased that we finally may be able to get some resistant isolates in setting up our breakpoints which will give us a much better understanding of how the drug in vitro breakpoints can be set having those resistant isolates and the clinical outcome with them.

[Slide.]

With this one, I would like to conclude my talk. I think this would address all the microbiological issues that we received from the industry and other bodies. I would like to thank my colleagues in the clinical micro group in the Division of Anti-Infectives, Dr. Albert Sheldon for his continuous support of the group--he is our team leader--Fred Marsik, Harold Silver, Peter Dionne and James

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King.

Thank you.

Panel Discussion

DR. CRAIG: Comments? Questions? I must admit that I still find it difficult when you are doing a double-blinded study and you have got an organism that is resistant to one drug and not to the other, and you don't know what drug the patient is getting--it makes it difficult, or I'm sure you are going to have situations where certain physicians, no matter how the patient is doing, is going to pull the patient out of the study.

So it is still going to make it difficult to be able to obtain information on resistant organisms when you are doing it in a trial comparing it with an agent that has significant problem against those resistant organisms. A class-A example would be for drugs against drug-resistant Strep pneumo and using some of our standard ones which I think there are clearly problems with many of those drugs.

It just makes it more difficult to get adequate numbers. Already, it seems that the resistant organisms disappear when everyone starts a clinical trial. Secondly, the difficulty in being able to enter the studies; the question is, do you decide certain ones like sinusitis where you are not going to see deaths occurring, whether that

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situation, you just let it go ahead and document it better, or do you do studies like we have talked about before, doing retap studies so you find out the information relatively soon so you can at least get some bacteriologic efficacy?

We just need to think of other ways that we can eventually design trials so that we can make it easier to get that information which I know is what you are hoping is going to be the plan for the October meeting.

DR. CHIKAMI: I think those points are sort of right on target. Part of it is a judgment of the risk of the result in failing therapy, as Dr. Altaie pointed out. It will be different for a study in meningitis versus the study of UTI.

The other issue is designing the protocols so that, in fact, there is a safety valve, if you will, in following the patients carefully enough so that if there is evidence of clinical failure that there can be appropriate change in therapy. That is adequately designed in the study and all that information is captured.

So those are some of things we need to consider.

DR. ALBRECHT: As you commented, it seems like sometimes the resistant organisms disappear when you are doing the clinical study. But in cases where we have had these situations come up, some of the options that were

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entertained, as Dr. Chikami said, if the patient were clinically doing well, there was a high level of attention to this discordance between clinical and resistance and the patient would be carefully followed.

But other approaches have been that the patients, actually, then get excluded from the blinded study and put on an open arm and followed to gather all the information because sort of the paradox was, when we were developing some of the cephalosporins for the bugs the penicillins didn't treat, it was like, "Well, I'm using the appropriate control and yet how do I prove my case this covers those organisms?"

So, having clear criteria of what would be collected on the patients in this sort of open sidearm was one of the ways we got at it.

DR. CRAIG: The other question that I would have relates more to breakpoints. NCCLS has gone ahead and put together their criteria that they require from industry and, at least the criteria on which they are going to base breakpoints, the M27 document.

Do you have similar things that industry knows that you require? Are they similar at all to what NCCLS requires?

DR. ALTAIE: Yes. We have a document in progress

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of being published that was put together with the microbiologic groups in the Division of Anti-Infective and Antiparasitics and Special Pathogens. So we do have a document that is going to come out and outlines our needs for the way we need the microbiological data to be presented, analyzed and documented.

The big issue, the difference, is that NCCLS, under the CBC influence, I think, is steering away from predicting clinical efficacy of a drug by setting those breakpoints versus predicting resistance. That is a philosophical difference and the breakpoints can be very different.

I think one big issue that needs to be solved between FDA and the NCCLS is that what are we setting the breakpoints to predict, clinical efficacy or rising of resistant organisms? I think that is the philosophical difference between the two agencies.

DR. CRAIG: That is a debate internationally as well. Some countries have set their breakpoints primarily just to pick up resistance and others do it more for clinical purposes. So you are right. It is a debatable issue. Both are important.

DR. ALTAIE: And we have to find a medium happy place to not have disparities with NCCLS.

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DR. RELLER: I wonder if the revision of the wording having to do with the ability of an individual patient to be continued who is doing well doesn't have a--whether or not it should be recognized, the real reason for doing that.

I have questions about doing it to get information on breakpoints for the following reasons. If the patient is doing well, and, in fact, the organism is resistant by current breakpoint criteria, what the NCCLS sees presented is that the breakpoints are wrong, based on a paucity of data and that they should be loosened.

So it works the other way around, that it doesn't have to be as susceptible as what the breakpoint is to still get a good clinical outcome. The numbers are never large enough to make firm conclusions. I fail to understand how a clinical trial that is ethical, based on inclusion of patients who have a reasonable probability of benefit could likely generate sufficient numbers to give you crisp data on failures related to resistant organisms because the numbers are so heavily stacked for susceptible ones.

Rather, the ability to continue a patient who is doing well, despite possible in vitro resistance at currently set breakpoints has more to do with recognition of good patient care and a little bit of flexibility in the

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process for carefully assessing the patient clinically and that the revision of the breakpoints, at least from what I have seen over the years at the NCCLS meeting, comes more from development of resistance that was not recognized earlier and seeing clinical failures that then one comes back and looks at patients who have failed, for example, patients with fluoroquinolone-resistant gonococci and then revision of breakpoints, or enterococci that the breakpoints weren't appropriate and have to be tightened up because patients are not doing well despite apparent in vitro susceptibility, or a methicillin-resistant staphylococci, coagulase-negative staphylococci, that there is a mismatch between some clinical outcomes and going back where the breakpoints were inappropriate and have to be adjusted.

But to get that information up front from a clinical trial that is predicated on giving patients drugs to which their organism is susceptible, I simply don't see how--it is not possible to have it both ways. It is not possible to do the right thing for the patient and get enough numbers of those that are truly not susceptible to be able to give you clinical failures which you would need to have to validate resistance.

So, theoretically, there may be a few mismatches but the very mismatches that someone would be likely to

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continue the drug would be where the patient is doing well and you would end up with a resistant-organism patient doing well, therefore, let's loosen the breakpoints and be more inclusive, which I think is not the wisest idea based on some of the--it gets us into the situation in this country of having too generous a criteria relative to, for example, what the Europeans look at in some of the breakpoints that have been said already.

Just another viewpoint.

DR. CRAIG: I understand the concern. My view on it, though, is that we have had breakpoints or we have had doses of drugs that we have used that have been real overkillers for what really has been required. So there is some fluff underneath there that can cover many of the resistant organisms.

Should we, though, still just call those resistant and entirely go to new, more expensive, agents and abandon drugs that have been around for a long period of time? I think that is when you have to weigh it.

If you are talking about a very expensive, potentially toxic, drug, playing around with breakpoints in that situation, I would agree with you. That is not the scenario that I would support as well.

But when we have tried and true, narrow-spectrum,

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relatively highly effective drugs that we have tended to dose too much in the past, at too high a dose, then I think there is some room to look at changing the breakpoints. So we try and get clinicians to use agents which we think are more narrow spectrum which result in less side effects than forcing clinicians to go and use newer drugs.

So I think you have to take both aspects in there and try and find a medium that everybody can come to a consensus.

DR. RELLER: Bill, could you give some examples of the cites--

DR. CRAIG: Let me just cite for amoxicillin. Amoxicillin is a drug which, if we use penicillin MICs for it, we would have a very high degree of resistance and we would not be using that drug. Most of the great majority of Strep pneumo would be resistant.

So what happened was, the first time around, we pushed the breakpoint from the penicillin breakpoint up to 0.5 for amoxicillin. Now, recently, NCCLS has been looking at it with additional data and moving it up a little bit higher.

So that is a drug which is a narrow-spectrum agent and one that has been around for a long time, has been the recommended drug of choice for many clinicians. So what we

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are trying to do is be able to use this drug as rationally as we can because of our good experience with it in the past.

So I think, for trying to find the right breakpoint for that drug, is a goal that we should look for.

DR. RELLER: For, like, respiratory-tract infections.

DR. CRAIG: Yes.

DR. CHESNEY: Which NCCLS is working on.

DR. CRAIG: Yes. But I agree with your point, too. But it needs to have some clinical data to back it up. That is oftentimes the hardest thing to get if you eliminate all resistant patients from clinical trials. It is very difficult to find good clinical data.

That is why the kind of data we have been able to model has been much more on bacteriologic data which comes from otitis media, sinusitis, those where double punctures are done, where there are diseases where, even with resistant organisms, you are oftentimes going to see a fair degree of clinical success.

But pneumonia is a much harder area to try and get that kind of data.

DR. ALTAIE: If I might chime in here. I also think that the breakpoints that were being set previously,

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we tended to set more drug-class breakpoints. Within the limits of the error of the test, 1-2 dilution being acceptable from day to day, that was a practice that would not have put us in this situation as much as we are in it now.

The drive for that is this percent susceptible for marketing purposes that drives companies to come to NCCLS with a limited amount of data and say, "Well, I don't think 0.25 is appropriate. If you put me at 0.5, my susceptibility is going to shoot up."

I think that game of one-dilution change and raising falsely the susceptibility or percent susceptible organism for a given drug has driven us into a situation where we really don't know what we are dealing with anymore in these breakpoints.

I think we should steer away from a one-dilution difference, changing the whole breakpoint, raise the susceptibility to what the company is happy with, and stick more with class breakpoints, if applicable. I understand that sometimes it is not. But when it is, I think that is a solution to put an end to this game.

DR. CRAIG: Any further comments?

If not, let's move on to the next one which is on clinical pharmacology. The FDA presentation will be given

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by Philip Colangelo.

Clinical Pharmacology

FDA Presentation

DR. COLANGELO: Good morning.

[Slide.]

This morning, I will discuss the major revisions that we have made to the draft guidance under section 6, now, clinical pharmacology and biopharmaceutics.

[Slide.]

Just to back up a bit, in the previous draft guidance document which was known as the evaluability criteria document, the section that we had was entitled pharmacokinetics under clinical issues.

[Slide.]

Currently, now, in the new draft guidance, the entire section has been renamed to clinical pharmacology and biopharmaceutics. The reasons for this change were really twofold. One, we felt that this more accurately reflects the content of the revised second and, secondly, it also reflects the approach that we, as reviewers in the Office of Clinical Pharmacology and Biopharmaceutics now take when we review submissions.

When I say submissions, I am speaking for all drugs and not just any infective drugs.

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[Slide.]

So, to expand on the concepts of clinical pharmacology and biopharmaceutics a bit further, the biopharm component of a submission can be thought of as a characterization of the drug product, itself, or the formulation, if you will, and also assessment of the drug product quality.

I have listed here primary areas of focus for biopharmaceutics. This really isn't anything new. It is sort of standard fare, if you will, for a submission. It includes evaluation of bioequivalence, bioavailability, the effect of food on systemic availability, evaluation of in vitro dissolution, and, perhaps, correlation between in vitro dissolution and in vivo bioavailability and other formulation issues that may arise.

There have been no changes with this section from the previous draft guidance.

[Slide.]

The clinical pharmacology component of a submission can be viewed as the characterization of the drug substance in humans. Again, I have listed the major areas of focus and they include evaluation of mechanism of action, pharmacokinetics, PK, pharmacodynamics, PD. If applicable, PK/PD evaluation. Evaluation of certain patient

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characteristics or demographics--that is, as covariates to explain variability in either PK or PD or both.

Evaluation of special populations and their effect on kinetics or dynamics, and this would include the elderly, pediatrics, renal and hepatic impairment. Evaluation of relevant drug-drug interactions and also a population approach. Population approach can be used to explore for relevant covariates again or to also discover or explore the influence of the covariates on variation in PK or PD.

Also, a population approach can be useful when there is sparse sampling such as in phase 3 trials to estimate pharmacokinetic parameters in the target population.

If I could just back up a bit, with respect to kinetics, pharmacokinetics, this, of course, is a characterization of the absorption, distribution, metabolism and excretion of a drug. This has already been discussed by Dr. Frank Pelsor in the previous advisory committee that was held for the previous draft guidance.

So there have been no real substantial changes to this section, either.

With respect to pharmacodynamics, in very general terms, pharmacodynamics seeks to describe the relationship between drug dose or drug concentration and pharmacological

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effect. For anti-infective drugs, here we are speaking of the rate of kill or the suppression of growth of microorganisms.

A combined PK/PD evaluation attempts, then, to relate an oftentimes mathematically model, the temporal change in the response with concentration. In other words, we are trying to quantitate the time course of the response with concentration.

[Slide.]

We have included a discussion of the PK/PD evaluation of antimicrobial drugs in the current version of the draft. Really, this represents the most substantial change that we have made to our section.

This discussion was included, in part, because of comments that were made to the previous draft guidance by the Society of Infectious Diseases pharmacists. Really, to summarize what they have said, they actually supported the use of PK/PD analysis as part of the drug development program for anti-infective drugs.

Also, we at the agency also recognize that this is an evolving area and that there has been rather extensively investigated in in vitro and in animal models of infection and increasingly in patients to assess antimicrobial activity.

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So the literature in this area continues to expand and, in some instances, supports the use of this type of an approach.

[Slide.]

So what could be some of the benefits for PK/PD evaluation? One would be that it could facilitate the early selection of a lead candidate. This would be such as doing preclinical screening to evaluate either an in vitro model of infection or an animal model of infection, the PK/PD relationships.

Another benefit, and a very important one that we see, would be that PK/PD evaluation can lead to the selection of an appropriate dosage regimen. This would be such as during your phase 1, phase 2 trials and, in turn, then would provide very valuable information to design your later phase 3 trials to assess pivotal efficacy and safety.

Another benefit is that a PK/PD evaluation may help you better understand either clinical or microbiological or maybe both outcomes. This would be such as during your confirmatory phase 3 trial. And outcome would be construed as either a failure or, perhaps, success.

So the net benefit would be a more efficient drug development program.

[Slide.]

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In the revised section, we discussed the PK/PD parameters that have been examined the most. These relate antimicrobial drug concentration or some metric of exposure to in vitro susceptibility of the target microorganism--that is, the MIC.

This is a table that I have taken from Dr. Craig's recent review article that appeared in Clinical Infectious Diseases which shows the common PK/PD parameters that have been related to antimicrobial efficacy with particular drug classes or certain drugs, parameters such as above the MIC which is the time that the drug concentration relative to the dose interval spends above the MIC may be related to beta-lactam-type antimicrobials.

Then you have the 24-hour area-under-the curve-to MIC and peak-concentration to MIC ratios which may be related to concentration-dependent killing type antimicrobials.

[Slide.]

These parameters have been correlated with antimicrobial efficacy mainly in in vitro models and in animal models. I think that is an important point is that they have been mainly correlated here with in vitro and animal systems. They have recently been related, in more limited cases, though in the clinical setting.

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There are other approaches and markers that can be used and have been experimented with. The bottom line, at this time, is that more data is needed from clinical trials to really adequately validate these parameters and markers and this would be especially as reliable predictors of clinical and/or microbiological outcome.

[Slide.]

So, to summarize, we have stressed again the importance of adequate clinical pharmacology and biopharmaceutics data. In the context of that, we have added a discussion of the PK/PD evaluation of antimicrobial drugs. Currently, we view it as an evolving science and, really, like pharmacokinetics, as a tool for providing an additional level of certainty and especially with respect to the selection of the optimal dosage regimen.

We would encourage increased utilization of PK/PD evaluation especially prospectively and, also, we would encourage sponsors to incorporate this type of analysis throughout their drug development program.

Finally, we also would encourage frequent discussions with the agency regarding these issues.

[Slide.]

Lastly, I would like to also acknowledge Dr. Frank Pelsor and Dr. Funmi Ajayi who have coauthored this section

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with me and have been involved in helpful discussions for this presentation.

Thank you.

DR. CRAIG: Any questions and clarification?

Committee Presentation

DR. CRAIG: Obviously, this gives me a chance to discuss my bias. I think this is a significant addition or at least a first step in the right direction in terms of changing or altering some of the guidelines. When one talks about validating PK/PD parameters, the ones that I show there, to find out which parameter is actually important, what you have to have is a lot of different dosage regimens.

If you primarily look at one dosage regimen and look at a higher dose and a lower dose, all the parameters are going to increase. You are going to get a higher peak level, higher area under the curve, higher time above MIC. So it is exceedingly difficult to try and pull out which is the parameter that is most important.

The only way that you can really do it is by doing multiple dosage regimens because then you vary the parameters and to do that in human clinical trials is going to be very difficult. But, clearly, what can be done is parameters can be determined in animal models of infection.

One of the things that is appearing to occur, at

at least I think it is fairly well documented now with the beta lactams is that the magnitude of the parameter required for efficacy in an animal model appears to be not species dependent. It appears to go across a whole variety of different animal models and also appears to be related to the magnitude required in human infections.

So the potential is to use animal models, and maybe this will also work out for in vitro models, to at least get a magnitude parameter that would fit with whatever MIC one is picking and using the MIC as your potency indicator and at least come up with the dose that people are using, what kind of MIC could you tolerate.

So I think it can be useful for helping to set breakpoints. I think it is going to be especially helpful as was mentioned in early drug design, to try and find some of your best candidates. I think it is also going to be important in drug development.

But, as was mentioned, what we really need is not just more animal data. What we need is a lot more clinical data. I think that is where we really need the partnership with industry for them to incorporate some of these pharmacodynamic studies into their early trials with new drugs.

Obtaining PK data, oftentimes population

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pharmacokinetics, is very nice because then, oftentimes, to generate that, you don't need a huge number of samples for individual patients. Then, with population pharmacokinetics, it is a very good tool that one can then use that to actually predict fairly accurately what kind of pharmacokinetics one is going to see in other individuals, and then start correlating that with response.

Many of you saw the article that Dr. Drusano put together in JAMA this year using such a technique with levofloxacin and, again, showing what parameters came out and correlated with the efficacy of that drug.

So the earlier this is done, I think, in the clinical trial, like in early phase 2, the earlier the chance it has to be useful to the pharmaceutical companies later on. I know what many of us that have our biases on that this might be able to do, but I think we are going to have to have more clinical data before to make the agency more confident with the use of pharmacodynamic PK/PD parameters before they will be able to start using them more in terms of the possibility of being able to reduce the number of patients that are required in order to put the whole document and get the whole drug through the agency and the review process.

We know that everything is very expensive to put a

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drug through and any tools that we can use to still make sure that the drug is safe and effective but to reduce some of the cost I think is a goal worthwhile trying to achieve.

So I think PK/PD right now is a potential chance to do that but what we really need is the clinical data. So I am pushing and suggesting that industry try and, whenever possible, incorporate some of these. I know many of the companies are starting to incorporate PK/PD studies into their early phase 2 trials in order to gain such information in the hope that, eventually, this will broaden our overall knowledge on this in the clinical arena and be able to be helpful for getting the drug approved.

DR. COLANGELO: Let me also add that FDA is putting together a workshop to discuss this issue and it will be upcoming.

DR. CRAIG: We also would let the people in the audience know that the International Society for Anti-Infective Pharmacology will be having a symposium at ICAC this year. It will be on Wednesday, September 23, the day before ICAC starts and the title of the symposium is going to be The Use of Pharmacodynamics for Drug Delivery and Drug Development.

This is a symposium, as I said, that will be at ICAC. So I think there are going to be these workshops and

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things around that I think, in the long run, will expand our knowledge and, hopefully, get more people up to snuff on what we are talking about.

Committee Discussion

DR. MURPHY: Thank you very much for your comments because I think you have put it very much in perspective for everyone. This is an exciting arena. Certainly this whole area has enabled us to move pediatric drug development along and I think it is an area that we would look into.

We always like data that enhances us and forms us and directs us. We just can't make quantum leaps and we need that clinical information.

DR. CRAIG: As the drug companies will say, there are always, among physicians, risk takers and those that are more conservative. Obviously, I am a risk taker but I think what you have to do--it is good to have both to make sure that a consensus comes up and there is good science that backs it up.

DR. GOLDBERGER: You were just talking about risk a second ago. Obviously, one of the ways to minimize it is to use some of the in vitro and animal models of which you spoke a few moments ago.

Since you have a lot of expertise in those areas, I was curious, are there any particular caveats we should be

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thinking about with particular models, particular drug classes, as we try to interpret that data or make recommendations to companies, for instance, in terms of using it?

DR. CRAIG: In terms of the magnitude of the parameter that is required for efficacy, I think there is fairly good concordance between animal models and what we have tended to see in humans in terms of the time above MIC that is required for penicillins and cephalosporins, carbapenems--not as much either animal or clinical data just with carbapenems.

What you need in order to really be sure that the magnitude is correct is you need failures. It wasn't until the penicillin-resistant pneumococci came around that we started to see failures. So then things started to look fine.

We have had many bacteriologic failures for a long time with Hemophilus but that is in otitis media, oftentimes in older kids where I have told you before the bacteriologic failure is infrequently translated into a clinical failure.

But there are magnitudes, I think, for certain drugs that have come out very well and it appears to be model-independent. By that, I mean what is required for pneumonia is similar for what is required for peritonitis

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models, the soft-tissue models, bacteremia models, so that the data is relatively tight.

It is very interesting. You can just go back to the old data in the literature and, as long as they give pharmacokinetics, you can sit down and calculate from the old studies in the literature. It is amazing how close and along a very nice line one finds all the drugs and multiple drugs within the same class fitting.

I would say that at least from the data that we have been able to put together, free drug levels appear to be the levels that one needs to look at. If one looks at a highly protein-bound drug, one finds that it requires a higher time above MIC than a drug that has low binding.

But if you correct for it and look at only free drug levels, then they seem to be roughly the same. So that would be one of the caveats that I think have come out of what levels should we be looking at. At least with the beta lactams, it looks like it is the free drug levels.

I can't tell you that is the case with the fluoroquinolones. There hasn't been enough data yet and it is only recently that we have started to have fluoroquinolones with higher degrees of protein binding. So that area is still a little unclear.

DR. GOLDBERGER: Is the degree of protein binding

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sort of species-independent? Is it constant across species?

DR. CRAIG: No. It clearly varies in species but you can use tricks. We are able to produce pretty close to human binding in mice by injecting human albumin and getting human albumin concentrations in the mice.

So there are ways of getting around that and showing that you can start to approximate what you see. But if you look at free drug levels in both species and look at its parameter, then that sort of takes away the problem with protein binding and the magnitude of the parameter seems to be the same.

So that is what is nice about it. If it was the total drug level, that was the parameter that was really correlating, then the degree of protein binding would really affect what the total drug level would be and make it much more difficult to look at that among animal species.

That still may be the case with fluoroquinolones. As I say, it is just more work needs to be done. Macrolides, while we know what the parameter is, the magnitude of the parameter required for efficacy is not as clear. So there are a variety of drugs still in which a lot more work needs to be done.

Keith and I are right now looking at a paper that has been submitted in vancomycin for glycopeptide. It is

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very difficult to try and figure out what the parameter is that is important for efficacy.

So I agree with you. We are far from being at the end of the tunnel and knowing exactly what we are doing, but I think there is enough data now at least, for beta lactams and fluoroquinolones, to suggest that the magnitude of the parameter found in animal models is very similar to what one sees in humans, that is is something worthwhile to proceed on and get more information.

I think NCCLS has sort of bought into it and now has added it as one of the other characteristics besides clinical data, population distributions, things like that that they will be looking at for breakpoint determinations.

DR. RODVOLD: One of the questions I had for your presentation, and maybe it is in the documents and it just didn't come across in your slides, is that--and we talked about this yesterday with one of the disease states--is the aspect of tissue levels. That would be another area that, if you don't have it, I would encourage you in the future to address, even in giving guidance to the sponsor of a compound as well as interpretation of that data.

There are lots of ways. It is important in the sense of knowing whether or not drug is in the tissue or in the fluid, but where do you go from there and what kind of

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guidance that they should collect, shouldn't collect, how to do the studies.

I am sure Bill would tell you that the literature is riddled with all kinds of data that you can twist the way you want it to say, but it may not be meaningful if it is not looked at the proper way. So I would encourage that because it is coming into some of the disease-state documents, not so much in abundance but it is still out there.

So if you haven't, I would encourage that as another thing. Actually, the approach that you have is probably the better way of looking at it at this time so you may want to use it as to get it out of the other places, but I think you will still be approached by, we are going to do this study, collect these, and we want it in our advertisement or--I think you have to be ready to look at that.

DR. CRAIG: I think you have worded it very well in here in what you are looking at in tissue distribution. Where you also say this does not imply that the adequacy of such testing methodology has been verified for all infected sites or that the relevance of all such data to clinical effectiveness has been established.

So I complement you on the way it is worded

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but--yes; I think we do need tissue distribution studies. There are new techniques now for looking at extracellular fluids, microdialysis. Some people now are even starting to do microdialysis in humans so there are ways of looking at concentrations at sites of infection that don't involve grinding up the tissue and mixing all the intracellular with the extracellular gemisch.

So, again, this is another area where technology is expanding and where we will have more information, and I am sure the kind of information you will eventually require will also vary depending on how the technology changes.

DR. SANDHAUS: Sandy Sandhaus, Nexstar. I had a pair of submitted questions, the first of which I think is most relevant right now. Basically, I am going to posit a theoretical drug.

[Slide.]

This theoretical drug is a liposomal aminoglycoside. The most important aspect of is probably the last one there; it has the potential to reduce class-related toxicities, this hypothetical drug, dramatically alter PK with an elimination half life of about nine days following a single intravenous administration, human safety at 1500 mcg/ml plasma levels of the parent drug, and efficacious in animals and some data in humans.

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But the MIC is not measurable and not predictive of the efficacy in these animal studies.

[Slide.]

So the question then is a simple one. What are the scientific considerations in designing clinical trials for antibiotics that cannot be evaluated by classic in vitro susceptibility testing?

It seems like the discussion they just had was extremely relevant to this.

DR. CRAIG: I can comment about another liposomal product, liposomal gentamicin, that we looked at in an animal model. Again, it didn't have as long a half life as nine days--was it nine days that you had there? But it had a much longer half life in the animal than the other drug did, probably about, say, 15 minutes to about four hours.

So it is quite a multiple increase. But when we calculated out area under the curve and looked at it in that regard for the parameter, the two drugs actually came out to be roughly the same. So that is the kind of thing that I would do in an animal model with this is try and find what magnitude of a parameter do you find for efficacy.

Oftentimes, people just study a drug so that it is efficacious but they never find the limits of where it starts to fail because when you start to find the limits of

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where it starts to fail, then it starts to give you a clue as to what the magnitude of the parameter is that might determine that and see if it is all related to what one sees that is required with a more standard formulation of the regular drug.

I think those are the kinds of things that can be done in animals ahead of time to try and get some information that might, then, be able to be looked at in a human clinical trial from the pharmacokinetics of the drug. The question is is what MIC do you use for the parameter. Do you use the MIC for the compound?

If it turns out, when you analyze the data, that you can use the MIC for the compound in the absence of the liposome preparation, then that is a clear advantage for you. Then you don't have to do separate MICs with this kind of drug.

So I think there are some things that can be looked at in animal models and using a variety of them to try and get a little bit better handle on what you might need to look at in a human clinical trial.

Any other comments? Keith?

DR. RODVOLD: No.

DR. CRAIG: What are the scientific considerations in designing? As I say, if you know what is required in an

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animal model in order to get efficacy against the pathogens you are going after and you know what that parameter is, then, theoretically, it will help you select what kind of dose you are going to go after.

Then, in an early phase 2 study, you can collect some kinetics in your patients, correlate your kinetics with the outcome in the patients in that dose and then start to get some initial PK/PD evaluation results. Hopefully, this will, then, enable you to decide on your final dosage regimen that you are going to use throughout the rest of the clinical trials and then things sort of fit into the regular ball game.

At least that is the way I would look at trying to take this kind of a product and work it on through and get it into the clinical arena.

DR. GOLDBERGER: I have a question. Have you shown, then, in other words, that this drug will work against organisms that a conventional amikacin dosing regimen would not work again, obviously, the amikacin dosing regimen to be given much more often.

One should probably distinguish between the issue of resistance and the issue which has been floated a lot with the liposomal compounds about an infection in an organ site or somewhere else where the distributional differences

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between liposomal and non-liposomal might play a role.

But, fundamentally, have you shown that it will work against highly resistant or resistant organisms where clearly conventional amikacin wouldn't work?

DR. SANDHAUS: The answer to that is that that is in process. The place that we are most actively investigating is--first of all, let me say that no organism has been identified that amikacin does not treat in vitro that this drug treats.

So, in other words, it has not changed the characteristics of the parent compound. But there are drugs an aminoglycoside treats in vitro that it is not used against clinically because of the low therapeutic index between where you get toxicity and where you can actually treat the drug; for instance, Gram-positive agents.

And this theoretical drug appears to be able to allow that therapeutic index to be greatly expanded. That is kind of the way I would put the current state of our knowledge.

DR. GOLDBERGER: Listening to that, it is a little less clear to me whether the issue, then, of using conventional MICs as a starting point won't actually work out. In other words, it seems that if you are not saying that we can treat highly resistant organisms, then it would

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seem as though the conventional MICs would at least be a starting point in terms of thinking how to proceed with the development of the drug.

DR. SANDHAUS: I can say that we have treated highly resistant organisms effectively in humans that have failed conventional aminoglycosides but the numbers have been extremely small. I am not willing to make claims for this drug that we can't support at this point.

DR. CRAIG: But, again, I would come back--I would think that there would be some PK/PD data that could be generated in animals that could be useful in looking at your Gram-positive organisms, finding out how much dose, what is the area under the curve, the peak level, all those kinds of things that are required for efficacy.

The problem that many people tend to do with animal models is to do one organism and, essentially, base everything on one organism while, in a clinical trial of 100 people, we may have 100 different organisms. So it is very important, I think, when one looks at animal models, that one looks at a variety of different bacteria so one can take in some of the variation that one would expect to see in a clinical trial.

DR. MURPHY: I would say that I think this fits in very well to what was my second slide with I think ongoing

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meetings with the FDA in your drug-development plan is a good idea.

DR. CRAIG: Yes.

If we have nothing more, it's break time.

[Recess.]

DR. CRAIG: We will move on to our last topic which is empiric therapy of febrile neutropenia. The FDA presentation will be given by Dr. David Ross.

Febrile Neutropenia

FDA Presentation

DR. ROSS: Good morning.

[Slide.]

As the last speaker, I was trying to explain to my son last night what batting cleanup means, but I am not sure I did a good job. At any rate, my name is David Ross. I am a medical officer in the Division of Anti-Infective Drug Products. I am going to be speaking on the proposed guidance for clinical trials of empiric antibacterial therapy of febrile neutropenia or ETFN.

One point I want to make at the outset is that I am only going to be speaking about empiric antibacterial therapy. Certainly, we recognize that antifungal therapy, given empirically for fever in the neutropenic patient, is an important issue but I will not be dealing with that in

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any great substance during this presentation.

[Slide.]

What I would like to do is talk about some disease definition and endpoint issues, describe the proposed criteria for conducting clinical trials for this indication and then finish with questions for the committee.

[Slide.]

Let me start by tracing the kind of shadowy outline of how the regulatory definition for this indication has evolved. Initially, this started out as the "immunocompromised patient," a phrase which appears in the labeling for drugs such as ceftazidine.

The problem is that we know that not all immunocompromised patients are alike. The solid-organ-transplant patient is not the same as the HIV-infected patient who is not the same as the patient on steroids who is not the same as the elderly, malnourished patient from a nursing home.

So, more recently, we have moved to the term "febrile neutropenia." This terminology has been used in drug labels for products such as cefapime and ciprafloxicin, but the process of defining this is still evolving, in part, in parallel with evolution in our understanding of the concept of fever and neutropenia.

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For purposes of this presentation, I am simply going to refer to this entity as fever and neutropenia, or FN.

[Slide.]

Why is it so hard to define this entity? What I would like to do is just describe some clinical scenarios that illustrate some of the problems in defining why it is hard to define these patients, both in terms of treatment and especially in terms of the setting of clinical trial.

As the first clinical scenario, I would like you to consider a 24-year-old woman with Hodgkins disease, an absolute neutrophil count of 0, and a temperature of 39 degrees centigrade. She is enrolled in a trial of empiric therapy of fever and neutropenia. Despite an intensive workup, no infectious source is found.

She remains febrile and neutropenic. Her antibiotics are discontinued after fifteen days. The patient defervesces two weeks later following bone-marrow recovery. And, following further chemotherapy, she obtains complete disease remission.

The question I would like you to think about is is this patient evaluable for efficacy.

[Slide.]

As a second example, a 47-year-old man with acute

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myelocytic leukemia develops fever while neutropenic. He also is enrolled in an ETFN trial. This patient promptly defervesces although, again, no infectious source is identified despite intensive workup.

Eight days into empiric therapy, the patient becomes febrile and hypotensive. He grows out multiple cultures of vancomycin-resistant Enterococcus faecium. The patient's antibiotic regimen is modified, but he dies from sepsis two days later. Is this patient evaluable for assessment of efficacy?

[Slide.]

Finally, on the next slide, consider a 70-year-old woman with stage 4 rectal carcinoma who is receiving irinotecan and 5-fluorouracil and who presents with a temperature of 37.1 degrees centigrade while neutropenic. She is screened for an ETFN trial that has an inclusion criteria of 38 degrees centigrade for fever.

She is enrolled by mistake. Blood cultures drawn at study entry grows Pseudomonas auruginosa. Repeat blood cultures at the end of therapy are sterile and the patient is clinically well. In a setting of this trial, is this patient evaluable for efficacy?

[Slide.]

I think that these scenarios, while they may not

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be typical, illustrate some of the problems in defining this disease state. Fever is not a perfect marker for infection in neutropenic patients. Not all patients with neutropenia and fever will be infected. Not all neutropenic patients with infection will have fever.

Blood cultures are an imperfect marker for infection in neutropenic patients. The majority of patients in recent series of neutropenic patients with fever have not had positive blood cultures. In addition, the interpretation of blood cultures can sometimes be problematic in the neutropenic host since these patients frequently do not show classic signs of inflammation.

Finally, fever is frequently not associated with positive blood cultures, as I have said.

[Slide.]

I think it is helpful, in some ways, to think about fever and neutropenia as a spectrum in which, at the top, we have situations where we have the strongest evidence for infection in which there is microbiologic documentation of infection, either with bacteremia or without bacteremia.

Below this, in terms of the strength of evidence, are those individuals where there are signs of inflammation or other signs of infection but we don't have microbiologic documentation, we simply have clinical documentation of

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infection.

Then, finally, there are those patients who have fever for which the etiology is uncertain. Sometimes, you will see this described as fever of uncertain origin. We know these patients may be infected. We know they have to be treated empirically to avoid early mortality, but we don't know if they truly are infected.

Finally, there are those patients who have fever that is felt not to be due to an infectious source, a bone-marrow-transplant patient with venous thrombosis, a patient with drug fever.

I think it is also useful to keep in mind that I am showing you a one-dimensional spectrum here in terms of bacterial infection. It is important to keep in mind that, in the real world, this spectrum has more than one dimension and that patients may also have fungal, viral or parasitic infections.

[Slide.]

This situation has led to a problem in defining febrile neutropenia for trials. There is a lack of consensus on who should be enrolled. In addition, the question of how you define the disease for efficacy assessment is unclear. Do you base this on those patients who you know have infection, on the basis of culture

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results, or everyone who enters on the basis of fever and neutropenia, which is the situation in the real world, after all.

[Slide.]

This has also led to a situation in defining endpoints for fever and neutropenia trials. There is a lack of consensus on how long patients should be treated before you can say whether the drug has worked. Should the primary endpoint be survival, regardless of what it takes to get there, so the patient can get their next round of chemotherapy or should we consider fever, the surrogate marker, as the primary endpoint.

The role of secondary endpoints is also unclear. What do you do with a patient who responds to treatment, as in the second case I presented, but then develops a serious superinfection. What do you do about new episodes of fever that may or may not be due to infection?

How are we to regard addition of other antimicrobial agents, in particular antifungal or antiviral agents or even other antibacterial agents with a different spectrum of activity. There are other secondary endpoints that one could imagine that I haven't put on here; for example, time to resolution of fever.

[Slide.]

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To show the kind of problems that can arise if the outcomes are not clearly defined in advance, let me present some data from Joseph Pater and his colleagues at the National Cancer Institute of Canada. They took data from actual clinical trials and said, "Let's see what happens if we change the outcome."

They defined one outcome as resolution of the initial episode with no new infection with a susceptible isolate. Under this definition, patients who developed an infection subsequent to resolution with a resistant isolate were still considered successes.

Outcome 2 was resolution of the initial episode with no new infection. And then, finally, outcome 3 was survival regardless of whether the patient needed to have modification of the initial regimen. So, for the first two outcomes, if you modified the initial regimen, you were considered a failure. For the third, it didn't matter as long as you survived the infection.

[Slide.]

They looked at three different regimens in a total of 283 patients. They found that the response rates for each regimen varied dramatically depending on what outcome you chose. The differences were also quite impressive.

For the first outcome measure, regimen C was

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clearly superior. For the third outcome measure, all three regimens did better than with the other outcome measures and the differences really weren't that great.

So one conclusion from this is that you really have to be careful of what you are asking in order to get usable information.

[Slide.]

To make the situation more interesting or confusing, this is not a static entity. There have been trends in empiric therapy of fever neutropenia that really have made life much more difficult for everybody. The microbiologic patterns of infection have changed.

There has been a shift at many centers from infection with Gram-negative organisms to infection with Gram-positive organisms. There have been changes in the practice of empiric antibiotic coverage with many clinicians using monotherapy in selected circumstances and, for selected patients, treatment with oral agents.

There has been an increasing use of growth factors which shorten the duration of neutropenia. Finally, there is data on treating selected patients who are felt to be at low risk for overwhelming infection as outpatients.

[Slide.]

In terms of how we can kind of put this altogether

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and try and aim at a moving target, I would just like to quote David Sackett here from a paper published almost 20 years ago in which he says, in part, "The answer to the question, 'Which events should be counted and which there should be blamed?" depends on the nature of the question posed."

I think we have to decide, when you are designing a trial for this indication, what it is we are asking the drug to do.

[Slide.]

Going back to the spectrum for this disease state, we know that, for microbiologically documented infections, we want bacteriologic eradication from the blood and clinical improvement. Going down to situations where you have fever alone, we definitely want to see defervescence. In all situations, we want to see prevention of mortality from the infection.

[Slide.]

So trying to put this together into a guidance framework for this indication, let me start out with the points-to-consider document which is incorporated in the current draft guidance. That suggests that an adequate and well-controlled multicenter trial in the setting of previously established effectiveness in at least three

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specific deep infections.

In addition, the IDSA guidelines published in 1992 made recommendations about the population to be studied, what modifications of the initial regimen would be allowable and what endpoints should be used and how data should be analyzed.

[Slide.]

So I think, to start out, in terms of who should be studied, clearly patients who have fever and neutropenia. We would define fever as an oral temperature of 38 degrees centigrade or more on at least two occasions or a single oral temperature of 38.3 degrees centigrade or more on at least one occasion.

The guidance refers to rectal thermometry. While we would not say that someone who had a rectal temperature taken that showed fever is not truly febrile, I want to emphasize that, on the basis of patient safety, this is not a method for taking temperatures that is appropriate for this patient population in general.

In addition, I want to emphasize that modalities such as tympanic thermometry raise issues about sensitivity with regard to detecting fever. There have been a number of reports in which patients who were obviously febrile were regarded as afebrile by tympanic thermometry.

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With respect to neutropenia, a neutrophil count os less than 500 cells per microliter within 48 hours of study entry would be considered evidence of neutropenia. Patients who are not neutropenic at study entry but have their ANC fall below 500 within this time period would be regarded as having neutropenia for study purposes.

In addition, the neutropenia should be due to an underlying malignancy or recent chemotherapy for such a malignancy.

[Slide.]

Additional information that we would want on these patients, and some of these factors are potential factors for stratification, would include patient age, would note that the IDSA guidelines call for stratification of studies: pediatric and adult populations; severity of depth of neutropenia; the nature of the underlying disease; hematologic malignancy; leukemia; lymphoma versus solid tumor as well as disease status; the use of growth factors, the presence of absence of an indwelling vascular catheter; the use of prophylactic antibiotics, and I will say a little more about this later on; if the patient is a bone-marrow-graft recipient, when they received it and what sort of transplant they received.

[Slide.]

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Who did we not want to enroll in these studies? Patients should not be getting antibiotics at the time that they are on therapy. We don't want to have the already confused situation with regard to treatment effect confounded by prior antibiotics within 72 hours of study entry.

This raises the issue of oral-antibiotic prophylaxis. In keeping with the IDSA guidelines, what we would recommend is that if oral antibiotic prophylaxis is used in a clinical trial, the regimen should be specified prospectively, the same regimen should be used for all patients who receive prophylaxis.

The study should be stratified prospectively according to whether or not patients receive prophylaxis. Finally, we would absolutely discourage the use of parenteral prophylaxis in the absence of a compelling rationale.

[Slide.]

Who else would we not want to routinely enroll in these studies. Patients with HIV infection represent a special category. I have put this in parentheses. It is not that we don't want information on these patients who represent an clinically important subgroup. It is important to keep in mind, however, that these are patients who

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frequently have clinically manifest immunosuppression due to their underlying HIV infection.

So unless the study is specifically set up to look at questions related to HIV infection as part of the study protocol, patients with HIV infection should not be routinely enrolled.

Patients with low-risk syndromes; for example, chronic benign neutropenia who represent a different population should not be routinely enrolled. Patients who are about to die from their underlying disease for whom assessment of therapeutic efficacy would be problematic at best should also not be enrolled.

Then, finally, situations where the pathogen has been identified prior to entry where it is not truly empiric therapy would also represent a patient population that should not be routinely enrolled.

[Slide.]

In terms of assessments, I think that these are fairly straightforward. Certainly, we want to know history, relevant review of systems with regard to signs and symptoms, physical examination. Culture data, obviously, is very important. Blood cultures including cultures from indwelling vascular devices and other cultures is indicated. Chest X-ray and other diagnostic tests is indicated.

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[Slide.]

Assessment should be carried out at study entry before therapy is received with an initial efficacy assessment at 72 hours when culture data should be available and a treatment effect might reasonably be expected to be manifested.

You would normally expect, in terms of subsequent assessments, that for inpatients, daily assessments would be carried out. For patients who are treated as outpatients under a protocol, the scheduled assessment should be discussed with the division in advance.

There should be an end-of-therapy assessment and then, finally, a test-of-cure assessment at seven days after the end of therapy.

[Slide.]

In terms of analysis considerations, assessment of efficacy should be done in a blinded fashion to avoid introduction of bias. This is true whether the assessor is within the agency or from the sponsor side. Analyses should include both intent-to-treat and per-protocol analyses.

Assessment of clinical response should be based on consistent application of objective criteria to the extent possible. All episodes should be analyzed if patients are permitted to be reenrolled. However, because episodes in an

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individual patient may not be completely independent of one another, a separate analysis should also be done for first episodes of fever and neutropenia.

[Slide.]

In terms of the populations to be analyzed, and I would just remind people of the discussion back on Wednesday by Dr. Lin and the committee, really, I think it is helpful to look at a number of different populations, especially in this indication where we may be interested in a number of different questions, so that no single population may give the answers that we need.

We would take all randomized patients and define a modified intent-to-treat population, and I will just remind you based on Wednesday's discussion, that by MITT, I mean that any exclusions are based solely on free randomization characteristics so as to preserve the randomization scheme.

We can also define a per-protocol population which is a less heterogenous population and, depending on how one wants to view it, a potentially more defined population.

[Slide.]

The MITT population would consist of all enrolled patients who receive at least one dose of the study drug, are febrile at entry, are neutropenic within 48 hours of entry, and do not have non-infectious fever at entry.

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[Slide.]

A per-protocol population would take those patients who satisfy the MITT criteria and analyze those patients who had at least seven days follow up, those patients who received the original regimen for at least 72Êhours without modification. Patients who were modified prior to 72 hours would not be considered evaluable under this analysis.

In addition, patients who die prior to 72 hours would be regarded as unevaluable in this analysis but considered failures under the intent-to-treat.

In addition, patients where there was modification for an adverse-drug reaction would also be considered unevaluable. If the patient had a fever of uncertain etiology and they receive antifungal, antiviral or antiparasitic agents, they would be considered evaluable only if that agent was given after they defervesced.

If they received these agents prior to defervescence, they would not be considered evaluable. Again, there would have to be absence of non-bacterial infection at entry. Finally, if the patient died before the test-of-cure, they would be regarded as evaluable only if you can attribute death to infection.

[Slide.]

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In terms of endpoint analyses, let me just quote from Walter Hughes and his colleagues in the IDSA guidelines. "It is optimal to use multiple parameters for the assessment of patients including clinical response to therapy, evidence of microbiologic efficacy and survival."

[Slide.]

I think what we would propose is to examine different endpoints as a matter of routine with the size of the analyzed population kept constant for any given endpoint for which success would correspond to specific clinical goals--i.e., survival, clinical and microbiologic response, the need for antibiotic modification and for protocols in which there was an IV to oral switch, what the effect of sequential IV oral therapy is.

[Slide.]

Definitions of response could include the following. The initial episode resolves with modification with no febrile episodes or infection before the test-of-cure visit. Under this definition, even if you defervesced, if you developed a fever before test-of-cure, you would be scored as a failure.

A less restrictive definition would simply look for resolution of the primary episode without modification of antibiotics. Under this definition, a new fever would

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not be counted as a failure.

Finally, the most lenient, or least restrictive, definition would be survival of the infection with modification allowed; in other words, prevention of early morality from infection.

[Slide.]

Other study considerations which should be discussed with the division in advance include the comparator to be used, treatment modifications that would be allowed during therapy, the use of oral antibiotics to complete therapy, protocols involving outpatient treatment, and planned subgroup analyses such as analysis of patients by severity and depth of neutropenia.

[Slide.]

Questions we would like to receive guidance from the committee on are first, are these entry criteria appropriate for studies of empiric therapy of fever and neutropenia, and how should protocols incorporated different analyses and different endpoints.

Thank you.

DR. CRAIG: Thank you, David.

I would like to acknowledge one other person that is at the table now and that is Dr. Arthur Brown, Professor of Medicine and Pediatrics, Memorial Sloan Kettering Cancer

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Center in New York. We clearly appreciate his being here because we do, as I say, need some expert help in this.

Maybe, Arthur, you might want to start off with what you think about the criteria that have been put forth.

Committee Presentation

DR. BROWN: I appreciate being invited to be here and to be a part of the discussion of this and will try and add what little I can to this. I first would like to say that I think that David's presentation has really brought together a lot of very complex issues and he has tried to put them, and I think quite successfully, in plain view for us.

So, David, I would like to acknowledge that it is obvious you have done a lot of work. I think it is very well done, at least put in front of us.

As far as Bill's question to me about these criteria and so forth, I would like to just comment that, unlike the other infectious kinds of definitions and things we use, as is plain to everyone, is an exceedingly complex thing because we are talking about a physiologic state. Even the definition of what is fever and neutropenia is so different, as we all know, than just the idea of having a microbiologically documented or defined infection such as pyelonephritis or such as--well, pneumonia, I won't get into

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because we could argue about that--but other kinds of infections, certainly meningitis or something like that.

From an oncologist's point of view, as well as an infectious-disease person's point of view, really, one of the things that, as David just pointed out, the survival of the episode is certainly a valid clinical accomplishment, where you want to get to and so forth.

But, from a regulatory point of view or design point of view or from a scientific point of view, that, obviously, is not all there is and there is a lot in between. So that is why this is so complex.

If I may, I actually want to comment on the wording, not David's wording because he was careful about it, but there is, in the literature, this term "febrile neutropenia." David got away from that and I would like to encourage us to get away from that because, to me, it doesn't make a whole lot of sense.

Neutrophils don't have fever. We should be callng it "fever and neutropenia" but not febrile neutropenia, or F&N or something like that, but not febrile neutropenia. I don't want to get into semantics too much, but I would like to encourage us to be using terminology that really is correct.

Another point is I would agree with David and I

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would encourage us not to even suggest that rectal temperatures should ever be a part of the evaluation of these patients because to put it in a guideline suggests codification and suggests that that is practice, and so forth, even though we may have "in parentheses" or an asterisk at the bottom of the page, we don't recommend this.

So if we don't recommend it, we shouldn't have it in there at all.

I am very in favor of the idea of multiple analyses as has been presented. I think it is very important to do it that way. I think there are, as has been said, multiple ways of looking at this that are essential from a regulatory point of view, from a scientific point of view and, obviously, from a clinical point of view as to what the outcome might be.

So it would seem to me appropriate that we recommend or try and structure, in terms of guidelines, the types of populations that would give the right kinds of accrual of numbers into the studies that would allow for the proper power of the study to be evaluated for these multiple analyses.

I will leave the design of that or how that is accomplished to the biostatistics people how we do that. That may be how we kind of come into some conflict of how

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this might be accomplished.

I am kind of the old-fashioned school that I sort of rely on the idea of a microbiologically documented infection even in the fever an neutropenia kinds of studies has to show me that, indeed, a certain regimen, regimenÊA, might be as good or better than regimen B.

I would bet that most ID people would subscribe to that kind of thing. But we all know that there certainly are the patients who, as was presented, don't fit. It just doesn't work out that way. That is the way the world works. It is not necessarily so.

So someone who defervesces but doesn't have even a clinical documented infection, that is sort of the next step down. Are they to be just tossed aside and not included? No; I don't think so. As I said, I think those people are just as important. So I think the multiple measures of the multiple analyses at those levels is appropriate, as David has presented them.

I think the question of not excluding HIV people from studies was well-handled by David and I said that I would agree that there are specific questions to be asked about these patients, especially the patients who have neoplastic disease who are HIV positive, like Kaposi's sarcoma patients, patients with non-Hodgkins lymphoma and so

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forth and so on.

They may well become neutropenic by virtue of the chemotherapy they get, not only because of the disease. But that is complicated and that probably should be in a special kind of area.

I am basically saying that I think what David presented is very reasonable. I actually had gone over it with him several times before and would acknowledge that. So I would go along with that.

Committee Discussion

DR. BROWN: Can you flip the questions back up there again?

DR. CRAIG: I tend to agree. I think the criteria, at least the inclusion criteria, seemed fine for me. The one question I have and I guess maybe somebody can clear this up for me, if somebody has, it turns out to be a line infection, are they excluded or are they included just as a documented infection.

The thing that I have always wondered is infected IV lines in these patients, is that a different entity than the other kind of infections that occur in these people and should they be looked at separately.

DR. ROSS: I think that is an interesting question. I'm sorry, Dr. Craig. Were you addressing that

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to me or to Dr. Brown?

DR. CRAIG: You can respond. I am addressing it to whoever wants to respond.

DR. ROSS: Oh, boy. I spoke too soon. I certainly think that, because this is an important clinical entity in this patient population, we need to look at those patients. I think there are a number of ways of doing that. I think that it may be helpful, as a planned subgroup analysis, to say how does a particular drug perform in patients who have line infections.

One thing I think we would want to see is a set of consistent results so that you had evidence of efficacy in the patient population with microbiologically defined infection, whether it was due to line-associated blood-stream infection or pneumonia.

I do think that that is a significant proportion in some oncologists' practices and maybe just about everybody will have these catheters. I think we need to look at those patients as a defined group.

DR. BROWN: Bill, that would be my thought as well. It is the exception rather than the rule that they would not have catheters. Almost everyone in the management of these patients now have devices of some sort for venous access. So, clearly, it would be an unreal world to

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separate them from the population being studied.

I understand your question. In other words, is it a different kind of infection from the point of view of the clinical kind of thing. It generally tends to resolve easily. It is managed easily and so forth and so on. So I think it would be a matter of designing things to take into account this type of infection, just like we might say the clinically documented or the microbiologically documented, the bacteremia, and then the bacteremia that is related to catheters without another source.

DR. NORDEN: I also want to complement David. I have one question and that is the test-of-cure timing. I think you proposed initially and said that whatever you do in this, it is relevant to ask what are we looking for, what are we trying to accomplish.

I am not sure that we are--frequently, what we are trying to do with the antibiotic therapy is to get the patient through, to, indeed, have them survive, to suppress whatever infection is there until their neutrophils were covered.

So, if that is accomplished--but if we wait seven days to evaluate it--this is different from strep pharyngitis or other infections where we are really going for eradication.

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I think what often happens, at least in our patients, is they become febrile again in that seven-day interval and you can't assess what it is due to. Then I think you get into the real difficulty of what do you say was the outcome of, or the response of, the initial course of therapy.

So I would propose, or at least raise as a question, whether one should shorten that period significantly.

DR. CRAIG: Isn't it a little dependent on when you stop therapy, if you stop it when the white cells are coming back as compared to stopping it when they are still neutropenic?

DR. NORDEN: Yes.

DR. BROWN: It certainly is and the other complicating factor is the growth factors at the same time because that has made even shorter the period of neutropenia in many, many of these patients. So there are multiple kinds of stratifications that you would have to do here to evaluate this--in other words, yes, getting growths, not getting growth factors, and so on and so forth.

I agree with you, Carl, that that was one of the areas where I didn't say it but David and I went back and forth in terms of a little bit on test-of-cure, really where

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is our endpoint in that regard and isn't it really the idea that patient is alive and well and moving on to the next round of chemotherapy or they achieved remission at the end of the day.

DR. ROSS: Dr. Norden, let me ask you--and I agree with you, that is a very real concern. One question I have is, given that you may want to put the test-of-cure--the time where you see a relapse may be influenced, in part, by the pharmacokinetics of the drug. Is there any way to take that into account?

This was one reason for picking that figure of seven days, but I certainly take your point that we are liable to have an unrelated event occur between the end-of-therapy and a seven-day test-of-cure.

DR. CRAIG: I can just tell you one of the interesting things working with animal models that you find, you can take Klebsiella and put it in the lung or put it in the thigh with a normal or a neutropenic animal and give the maximum drug you can give, you won't sterilize that tissue.

The organism still stays there. That's true whether you have got white cells or whether you don't have white cells. So the antimicrobial effect is essentially the same. But when you stop therapy, and the animal is still neutropenic, those organisms can come back while, if you

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have got adequate white cells around, they are sufficient to prevent that infection from coming back.

So that brings up, as Carl is saying, the evaluation period. If the patient is no longer neutropenic, I have no trouble looking at it out at a little longer. On the other hand, if you are stopping the therapy when the patient is still neutropenic, and you are looking at the seven days while they are still neutropenic, depending on what type of organism was the initial infection, there is going to be a good likelihood that you might see a relapse during that period of time and that, then, that is really not saying that the drug wasn't working.

It was working just as well as probably in the patient that doesn't have a relapse. It is just that the environment at the time that the therapy is stopped is a little different when you have white cells around and in the other one, you still don't.

So it makes it a little tricky. But if most of the studies are done and the therapy is stopped and the white cells are coming back, I do not have a problem with going out to a little longer time for evaluation.

But if it is that they are stopping the antibiotic relatively early and then one is looking at evaluation while the patient is still neutropenic which might happen in

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bone-marrow transplants, those kinds of situations where the neutropenia may be around for a longer period of time, then I think it does become a little trickier.

DR. GOLDBERGER: Have you noticed any meaningful differences, at least in the models, in how different classes of antibiotics or antimicrobials might perform once the drug is stopped in terms of the period of bounce-back of infection?

DR. CRAIG: No; we have not seen any different between beta lactams, aminoglycosides or fluoroquilolones.

DR. HENRY: Dr. Craig already touched on this, and following up on Dr. Norden's comment about when you do the test-of-cure, actually I think the greater question is when do you define end-of-therapy? Again, you can stratify for whether or not white cells are there, but it gets very complicated if you have a predefined end-of-therapy assessment and you think someone's white count is coming back.

We have all seen it happen. All of a sudden, you see the monocytes come back and you think, "This is it. Tomorrow, there are going to be neutrophils," and then you find out that it cycles back down. So how do you define end-of-therapy?

I think you are going to have to stratify by

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whether or not white cells are present or not present and not say, "Well, it is 48 hours and we think they are coming back." So you can't even talk about test-of-cure at seven days because I don't think you have clearly defined when you can end therapy without, again, taking into account what the white cells are.

DR. RELLER: Is it possible to put up slide 22? It is the timing of assessment.

[Slide.]

The terminology here is similar to what we have had for other infections where we had a site and an organism. Do we need a whole new paradigm or different paradigm for these assessments, the end-of-therapy?

I know there are some variations in practice, but the commonest scenarios, I think, are the patient becomes afebrile and then there is some duration of therapy and some people are willing to stop if there has been a period of being afebrile before the white cells come back.

Others, that is a great outcome and would continue it especially if there has been a response in terms of defervesce until white cells come back. I think the commonest endpoint is to change, ideally, if one has disclosure of infection that you usually don't have, but that the commonest endpoint is when the white cells come

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back.

I wonder if it wouldn't be more reasonable to have assessment periods related to what actually is looked at. Defervescence is one; some period after defervescence. Return of white cells above some number. And then a test-of-cure at seven days post-therapy.

Again, it depends on what the endpoint for the therapy is. I don't know if there can be a test-of-cure if you don't have something that you have potentially cured. I look at this whole process of being a therapeutic intervention that everyone accepts works, of if you don't do it, it is a grave risk for the patient.

But it is a holding action, a salvage, a forestalling, a hanging-on until the important elements return that we enable one to cure something if it were present with antimicrobial adjunctive help.

So I think it might be better to try to define reasonable assessment points based on objective events that happen having to do with temperature or white-cell return.

Art, what do you think?

DR. BROWN: Barth, I think you raised it in a very, very nice, clear, crisp way. What I was saying in the beginning remarks was that this is a more physiologic kind of disease state rather than defined always by specific

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pathology.

If I can use an analogy, we, the clinicians, are the Dutch boys with our finger in the dike holding back the sea. Essentially, when the neutrophil counts comes back, we take the finger out of the dike, stop the antibiotics. Usually, it works out well then.

So, really, your point about saying maybe we ought to have a different paradigm or a different way of looking at this in terms of what is not the classic test-of-cure as represented in the other kinds of things, it is probably a reasonable thought.

I like the idea. I think it requires some sitting down and trying to work it out. The details might be a little more cumbersome but the concept is a good one. It fits a little more, I think, how Carl and the rest of us have sort of been talking about this and it brings it together in the nice way.

So I would be for it.

DR. RELLER: One of the purposes, I take it, of this sort of forum is to not just say yes or no but to think about what the options would be. For example, in other infections, recognizing that there are different durations of therapy, and this may be a dramatic case of widely differing and, appropriately so, durations of therapy but

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for different reasons, of looking from the initiation of treatment and then some time period instead of after so many days after completion of therapy, so many days assessment after beginning of therapy. This has come up with other indications.

One possibility would be how long do these patients literally last after initiation of empiric therapy whilst neutropenic, so days below 500 that one survives after initiation of empiric therapy, because the empiric therapy may be a week, ten days, 14 days, empiric therapy cetera.

What one is really trying to do, it seems to me, is to acquire more days without neutrophils that one survives with or without fever, ideally without fever, because it just makes us more comfortable, until the stimulation of the marrow facilitates return that may be accompanied by fever, itself; that is, the therapies, the interventions.

But, in the end, it is keeping people alive who don't have neutrophils without which we know that, ultimately, we can live.

DR. BROWN: Where it gets very complicated and I'm sure I'm not saying anything that is news to anyone at the table is just let's take and AML patient who is going to be

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neutropenic for, potentially, as long as four to six weeks, which is not uncommon in our institution where people get very aggressive chemotherapy, and in other institutions as well.

So while you might start with regimen A at time 0 when they became febrile and neutropenic and by day 3 or 4, you have made some kind of modification, maybe adding a glycopeptide and then, by day 4 to 7, you have moved on to the antifungal therapy, perhaps amphotericin B or something like that.

They are going to remain neutropenic and there are going to be the superinfections, all through this time of many, many weeks. How do we score that? Again, in the spirit of just putting things out on the table--I don't mean to make things more complicated--that is where this gets very, very messy.

It is ont going to be a nice, neat kind of--and there will be much variation from patient to patient.

DR. RELLER: One possibility is recognizing that is what actually happens, is assessment points at times when people are getting only this intervention without additive therapies, and days. I think one of the differences, in terms of response, is whether or not one defervesces and you buy more days until you have to do something else.

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That might be a measurable endpoint--not a measurable endpoint but a measurable assessment point.

DR. BROWN: I like that in the sense that--I agree with you. In other words, if you had regimen A compared to regimen B that was started empirically initially, and it turned out you didn't have to modify at the third, fourth, sixth, seventh day but extended that, that might well be a measure of some validity of that regimen having been better. There is no question about that.

When we talk about test-of-cure and further down, it may well be that you are going to talk about somebody who does survive the six weeks and you wait for seven days after you stop something like that, is that really measuring what happened from the first time 0 to whatever time until the modification was made?

I don't know. It just gets messy. And are we going to have enough homogeneity in the study population to be able to say, "Yes; we had significant numbers in each of these regimens, and so forth, to compare A and B."

DR. NORDEN: I think what Arthur just said is very important, but just flip up slide 29, which is the definitions of response.

[Slide.]

As you look at them again and what are the goals,

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sort of the working definition--and, Arthur, correct me--that ERTC has used with some success, I think, is No. 2 which is that the episode is resolved without modification of antibacterial therapy but you are allowed to add amphotericin or whatever else it is because that is the real world.

You can't prohibit amphotericin therapy in a clinical trial. To me, if you can define the primary episode which is the febrile episode and then resolved is usually the patient has become afebrile. I think the first definition is impossible because you are not asking whatever antibiotic you are giving to prevent further episodes.

The third is, I think, as important; survival, also. But I think if you have modified the regimen, then how can you say that it worked, or didn't work. So I think your No. 2 is where I would go.

DR. ROSS: I take your point. I think that part of the intent of definition--and I absolutely agree with you--definition 1 is really asking a lot of the drug. It is asking it to have a prophylactic role which is a can of worms that I won't even begin to open because it is impossible to get them back in the can.

I think the idea with survival of infection is really prevention of early mortality. That is really the

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goal there and maybe we need to think how we would--

DR. NORDEN: As you said, you can have more than one endpoint. Survival is certainly something we want to look at. Resolution of infection. Death is not as good an outcome, obviously, as resolution and survival. So I don't think that either of those are mutually exclusive.

DR. MURPHY: That is also very important in looking at the other side of the equation which is the safety-toxicity issue that you may be picking up here also.

DR. GOLDBERGER: Also there have been some products reviewed and at least one approved, a lipid amphotericin product for a similar indication. One of the things that we tried to do during the analysis of that data, from actually a couple of different products, was to get a better handle on the data, we tried to look at the groups of patients, for instance, who did not require modification of antibacterial therapy while on the lipid amphotericin product or the control arm.

Also, I think, perhaps, more importantly, we tried to look at the group of people whose white count did not come back up to the normal range during therapy. There are problems, obviously, with doing all these subsets but, first of all, you get a better feel for what is in the data.

If you had a clinical trial where 80 to 90 percent

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of people had their white counts return to normal during therapy, you might not be sure how effective whatever the new intervention really was. We found it helpful to get a feel for how much data there was for some of the patients, in fact, who didn't really return to normal.

With at least one drug, there were some patterns that suggested that, perhaps, in those groups of patients which were a harder test for the drug, it did not perform as well.

One of the tricks with the lipid amphotericin products is one is not entirely sure what is the appropriate or equivalent dose, say, to amphotericin. That is probably less of an issue, hopefully, with some of the antibacterial, or at least it is easier to study with the antibacterial.

But that may be something else to consider about at least thinking about some of these subgroups in terms of getting a better handle on what the investigational therapy is actually doing.

DR. BLACKWELDER: With regard to the second endpoint and the discussion about it, I wonder if it would, then, make sense to think of the evaluation as being something like the time until there is no longer a fever rather than at some arbitrary time such as seven days.

Is there any thought about that?

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DR. SOPER: One of the objective criteria we have used in treating post-operative infections has been the so-called fever index which is the time of which the temperature is greater than 99 degrees and it is calculated through a formula when temperatures are taken, I think, every four or six hours. That might be another way of kind of looking at overall response.

DR. CRAIG: The title is "fever and neutropenia;" am I correct? At least, that is what we are trying to cure, isn't it? I think it is always hard. These patients can vary so much in their response, probably, to the same infection in terms of their febrile response that it may be difficult.

But if you have large enough numbers and they are randomized, that might fall out.

Other comments?

DR. GOLDBERGER: Going back, again, to the follow up on what you were just saying with regard to the lipid amphotericin drugs, one of the obvious original endpoints in those trials was resolution of fever. One of the problems, of course, not surprisingly, we discovered is that because there were so many causes, we couldn't really get a handle on to what was going on and you would see similar degrees of resolution of fever.

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But, in the first drug to be studied, the trials were small and actually we got very few microbiologically confirmed endpoints. A larger clinical trial was done. It was done by the Mycosis Study Group with more rigorous endpoint criteria. Actually, there, we found a noticeable difference in microbiologically confirmed endpoints, which I think people were somewhat more comfortable with than just relying solely on changes in fever during the course of the clinical trial.

DR. CRAIG: It is a chance, obviously, to get information on response in some of the diseases, the other diseases we see, pneumonia, things like that, in neutropenic patients which are, oftentimes, excluded from other clinical trials. So it is, I think, useful to try and incorporate that into the evaluation somehow, of looking at those where it is clearly both disease and microbiologically identified.

DR. CHESNEY: One of the advantages of having St. Jude nearby, or disadvantages, is that the rest of us no longer manage these patients. So this may be a question that everybody knows the answer to, but what is the quality of the neutrophils that are induced by the growth factors? Are they of the same quality in terms of responding to infection as the patient's own neutrophils without growth factors?

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DR. ROSS: I think I will defer to Dr. Brown on that question.

DR. BROWN: I don't know if I can comment on this, from the literature on this, for you, Dr. Chesney, but I don't have any reason to believe that there is any qualitative difference. I am struggling a bit here. I am looking to my colleagues around the table to see if they have any recognition of any laboratory data that supports or doesn't support that notion.

Carl, does it come to you?

DR. NORDEN: No. I have no data, but that never stopped from saying something. It is, just, again, reasoning by analogy which is that, in general, most hematologists say that if you have a neutrophil, it functions, and that we give--there, obviously, are diseases where it doesn't, but you give transfusions, for example--you used to give transfusions from leukemics and the mature white cells do function as mature white cells.

I can't speak specifically, Joan, to your question, though. I don't know the answer.

DR. BROWN: The only reason I was wincing, Carl, was not in response to your comment but I have had many oncologic colleagues who have told me they have "functionally neutropenic" patients, not receiving a growth

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factor, but they say, "We want to start them on antibiotics because they are functioning neutropenic even though they have the numbers."

I think that is probably where Joan's question comes from. I don't know how they know this.

DR. CRAIG: Let's look again. I think, at least in terms of entry criteria, everybody was satisfied with the entry criteria.

DR. HENRY: Just one question as far as clarification. You just said two temperatures above 38. Are you going to put a time frame on that?

DR. ROSS: The time frame that I think is in the guidance right now, I believe, is 24 hours.

DR. HENRY: So it was just not on the slide, but it is not changed from the guidelines.

DR. ROSS: Correct.

DR. BROWN: In the IDSA guidelines, was it a little shorter than that? Was it within six or eight hours?

DR. ROSS: Twelve.

DR. BROWN: Twelve? Anyway, it is written down somewhere that it is within a certain time frame. Apropos of talking about time intervals, David, can you help me? The 48-hour interval that you have to have a neutrophil count less than 500, is that also prescribed in a specific

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guideline or is it 24 or--

DR. ROSS: I do not believe it is in the IDSA guidelines. It should be in the guidance document.

DR. BROWN: I have my sort of gut reaction to this that it should be shorter. But I would be interested in other comments. In other words, you enroll somebody and you would like them to have their neutrophil drop down to below 500 within a certain period of time. 48 hours sounds a little long to me, but I wouldn't quarrel with it.

DR. RELLER: The IDSA guidelines simply say, "expected to fall," but it doesn't say how swiftly.

DR. ROSS: The derivation of that was to avoid a situation in which--we have seen where a patient is febrile at study entry but not neutropenic and then their neutrophils don't cross that magic barrier until four or five days later.

I agree. I think it is difficult to know where to draw the threshold.

DR. BROWN: For continuity, for homogeneity, for study purposes, four or five days in my mind is too long. I think that is easy to say. In our institution, the way we do it is we use 1000--just plain use 1000 because everyone is on this steep curve and they are sliding down very quickly. That is because the next morning, when you do the

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next CBC, after admission, they all have counts that are down 200, 300, even though they were just, say, 899 on admission.

They are down that low the next morning. So I am looking to a period of time--I think the point that was made just now about the time intervals, we ought to say discrete time intervals. Even if we have to be arbitrary, it probably ought to close in a bit.

DR. ROSS: So you would advocate a shorter interval of 24 hours.

DR. BROWN: Yes.

DR. RELLER: Another reason for doing that is the studies going back to Carpenter, Wintrobe, others, the half life of a circulating neutrophil is very short; five hours, six hours, something like that? It is very short. Particularly if one is looking at duration of neutropenia, it actually becomes very unfair if the drug evaluated has already got two days when the patient is not at risk versus another patient who plummets within six hours.

And there could be substantial differences where days and hours become important. So what, Art, do you think would be the most sensible time period when you are anticipating?

DR. BROWN: 24 hours.

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DR. CRAIG: So 24 instead of 48?

DR. BROWN: Yes.

DR. CRAIG: Good.

DR. HENRY: Bill, I had just one other question about inclusion criteria.

DR. CRAIG: Sure; let's work on the criteria.

DR. HENRY: Talking about blood cultures, we talk about at least two blood cultures of which one comes from a peripheral site. What do you do about all these patients who have double-lumen catheters? I think, if you have got a double-lumen catheter, you should be sampling both ports and, if you want to do a peripheral on entry--I guess if we are going to try and come up with things that are at least specific, now is the time to do that.

DR. ROSS: I think that is a n excellent point. I agree with you. I was thinking of this primarily in terms of devices such as Port-a-Caths. But if you are thinking about double-lumen Hickman, I absolutely agree with you.

DR. BROWN: I am going to bring up something that has to do with the economies of things in terms of bacteriology laboratories and so forth. I am hoping Barth will come in on this, too.

When we have triple-lumen catheters, we end up having four blood cultures. This has ended up being viewed

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as an unnecessary expense--well, "unnecessary" may be a strong word--but an expense that people would like to control in view of the times that we are in.

So it is discouraged, these days, from that point of view, at least in our institution. That has been discouraged, actively discouraged, to draw multiple cultures.

One could say the initial set of cultures maybe you should do this, but, certainly, to keep sampling again and again and so forth--in fact, one suggestion had been that people combine a sample from all these so at least you would know whether there was a positive culture.

I was an advocate of doing this years and years and years ago. I have to sort of close my eyes to this a little bit. I wonder, Barth, you are mainly a lot in the clinical microsphere, are you under similar pressures?

DR. RELLER: Yes.

DR. BROWN: Or do you pressure your clinicians to not draw as many cultures?

DR. CRAIG: He does the pressuring.

DR. RELLER: I wanted to come back to comment. Here is where I would like to be educated. I am not aware of any rigorous assessment of the utility of sampling multiple lumens in a multi-lumen catheter. There, clearly,

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is a relationship between volume of blood culture and sensitivity, but what does one do with the information if one lumen is positive and the other lumen is not positive and, given the continuity and the way these things move, particularly the organisms that are associated with these catheters in terms of biofilms?

In pediatric patients, who may have multiple lines, they are all touching each other. It is hard for me to imagine that what is in one lumen is not in contact. So I don't know where the data are that sampling one or the other or both or all--there are patients who literally are transfused to be able to obtain the blood cultures that are obtained when one gets a customary volume from each of the lumens and does it repeatedly of what is tantamount to surveillance cultures.

The volume blood that we receive on some of these patients is startling in amount and, literally, if you calculate it out, they have to be transfused, particularly in the children. So there has been a dramatic cutback in our bone-marrow-transplant units.

Frankly, when we get multiple lumens in our own laboratory--now, admittedly, I don't necessarily have the data on the other side, although this is something that we are in the process of analyzing now, we report it as the

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catheter-positive and do not issue reports from different lumens even if they are collected that way.

So there is a composite report, this patient's catheter, or blood drawn through the catheter, is positive for whatever organism. And then one gets into the dilemma of how those data are interpreted. Sometimes, the interpretation, I think, is dependent on corroboration with a peripherally obtained culture.

There are multiple, multiple scenarios and, also, it depends on what the organism is. If one grows from one, two, three or all lumens in repeatedly bacillus or yeast, I think the die is pretty much cast as to what needs to be done. The spotty intermittent coagulase-negative staphylococcus from one or the other lumens in someone who is otherwise doing--I mean, it becomes exceedingly difficult to interpret.

But I don't know of data that documents the utility of independently assessing different lumens and how that is all put together. But I would be delighted to be educated if that has been done and how well it has been done and where it is peer-review published.

DR. HENRY: Having been trained in blood-culture methodology and blood-culture studies by John Washington, I guess I brought an approach to my taking care of hem-onc

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patients with fever and neutropenia perhaps a little bit differently than some of my colleagues, and certainly different than some of the oncologists.

It really is a bit confusing and there really isn't anything that I am aware of published in the literature. It really, to some extent, may be common sense in trying to integrate the variables, especially of volume and number of blood cultures, in trying to best define how to take care of a patient.

Certainly, the house staff in pediatrics has heard me get up on the soap box about blood-culture methodology because, for so long, in pediatric patients, they weren't even taking sufficient volume that you had a credible culture.

So I think you bring up a number of issues. Not to belabor the point, I will try and address some of them. I think that in patients, and, again, we certainly see this among the bone-marrow-transplant patients and the AML patients, they have double-lumen catheters.

My own feeling is I want to know what is in the blood, so I want a certain volume and I want a certain number. I, personally, would be fine with both those blood cultures coming through ports in the line, not just because it is easier for the patient in terms of eliminating a

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venepuncture, but it satisfies the criteria of volume and number.

It also tells me whether or not one port or the other may be the colonized port which may be academic in the end, but we certainly have seen that where someone comes in and we will have a peripheral and both lumens cultured and only one lumen is positive.

It becomes important, as a reminder to the nursing staff as well as the house staff, that they have to alternate lumens in which the antibiotics are infused. Sometimes, that gets to be a little bit difficult if there is something running in a line like TPN that is not compatible with the antibiotic and you have to remind them that they have to switch and put infusions of antibiotics in both ports, whether they infuse on a daily basis or an every-other-dose basis.

So I think it is important, at some point, at least when they first come in, to know what is in both lumens. As far as once they are on therapy and we need to sample blood to see if they are bacteremic with another febrile episode, personally, I don't want a peripheral blood culture.

Again, it comes back to wanting blood, wanting the volume, wanting the number. You can certainly separate when

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you draw those blood cultures by several hours because I don't want blood through a lumen that just got a dose of antibiotic.

So I think that goes into your question or concern about how much blood we are drawing. John Washington established, back in the late '70's, that there was an upper limit to how many blood cultures could be drawn from a patient. Certainly, in pediatric patients back in 1991, we implemented guidelines that the volume of blood drawn is a function of the weight of the child.

You can, certainly, by physician discretion, say that you want a lesser volume based on the hemoglobin of the patient which, certainly, fits in well with the oncology population. So you can get the variables of number. Maybe you are compromising volume but you are still able to get, I think, more useful information.

Going back to your original question is there data published that says you have to sample both lumens and how do you report this, no; I don't know of any.

DR. CHESNEY: If I could just add a comment, now, about the febrile neutropenic child, but we have followed many children who had most of their bowel removed at birth and who are now 12, 15, years old who are totally dependent upon double-lumen catheters.

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I have followed a number of children who had one lumen infected and not the other, and we could easily reproduce that with repeated cultures, and peripheral cultures were negative. So if that is true for the febrile neutropenic patient, then it might be important to get cultures from each lumen at initiation.

That's just a comment.

DR. RELLER: I am a realist about the difficulty of access. I think it is better to have the appropriate volume of blood culture through a catheter than to not have a culture, to document interpretable pathogens.

What I have questions about is what one can tell from the commonest scenario, by far, by a log of having a coagulase-negative staphylococcus, sometimes a viridans streptococcus, from one or the other lumen with our without any peripheral blood culture and what one practically does about it.

There is no question that the best practices, best clinical practices, in the care, the infusion, the way the catheters are maintained as lifelines are exceeding important.

The numbers of organisms are small, and whether the positivity of one lumen or the other is a function of distribution of organisms, whether one can systematically,

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you might say, sterilize one lumen and treat a lumen as opposed to treating the patient, this is where it gets to be more complex as opposed to saying, "This patient has a catheter. We have a coagulase-negative staphylococcus from one lumen. This catheter is infected. We are going to take this approach and see how this patient does," and use the catheter as an access for repeat adequate-volume blood cultures to assess superinfection with Candida glabrata or whatever it is, whatever the resident most-common superinfection in patients that break through the empiric therapy or even the specific therapy for coagulase-negative staphylococci that may be added when there is a reproducible isolation of that organism which, I think, is the accepted grounds for intervening with vancomycin nowadays.

DR. HENRY: I would say that we don't say, "This is a red-lumen catheter-associated bacteremia." It is a catheter-related bacteremia. The point about sampling both lumens is so that you might know what is being harbored because, you are right; if it is in one lumen, ultimately, you can end up getting the other lumen colonized, just like if it is in the lumen, then you might have a peripheral blood culture as positive.

I don't feel any sense of comfort having just a lumen-drawn blood culture positive and a peripheral being

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negative. Positive is positive. That person is still at risk for that organism. So I don't think we differentiate in that regard. I think it does serve as a vehicle in which to obtain a blood culture specimen.

You are right. You can better satisfy, perhaps, the criteria of volume by drawing it all through one or both lumens. But, again, I also think it serves a reminder to people caring for the patient that you have to infuse the drug through both ports, whether or not you find that one port is positive or not.

DR. RELLER: I agree with you completely on this point. That is why, frankly, in our place, and we work very close with, particularly, the bone-marrow transplant unit, and that is it makes sense to me--it is fine to sample the catheter, what I would frankly do. It achieves the volume. It doesn't defeat the sensitivity.

Sample all lumens. Put them in the same bottle. Culture the thing and call it a positive catheter. What I don't think there are data for, or a least I would like to see, is that delineating which color lumen yielded the positive gives information that enables lumen-specific interventions that are lasting; namely, it is the catheter that is colonized and it doesn't make any difference from which lumen the colonization originated.

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DR. HENRY: Ultimately, it doesn't.

DR. RELLER: The implications of trying to keep all these separate and the poor sampling that derives and the number of cultures and the costs that are amplified, it gets to be counterproductive, I think, as opposed to saying, "This catheter is colonized. This patient is at risk and this is a grounds for when reproducible, intervening, over and above the empiric therapy that is already underway.

DR. CRAIG: Same reason as I mentioned earlier. I would still feel that you have to have the peripheral because if you don't have the peripheral, in my mind, the case is tossed out. It is not a real bacteremia.

Sure; you are going to toss out some that may be true bacteremias. Volume might have been a problem or there was a relatively low-grade bacteremia, but I think if we are trying to look at this entity, we have to have the peripheral blood culture.

DR. BROWN: I would agree with you, Bill, that you need the peripheral. The original recommendation was a peripheral and a catheter blood; right, David? I would suggest that we stay with that and the reason would be that the question you raised earlier, how do we differentiate and do we differentiate these catheter-related bacteremias from other kinds of bacteremias, we would be lost if we didn't

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have those two different things.

DR. RELLER: I would like to amplify on that. To me, in reality, the biggest problem, far and away, is coagulase-negative staphylococci in relation to these catheters, having, I think, reached a consensus on the meaning of the lumens, recognizing that it has not been rigorously looked at and published.

But they are taking the next step. The solitary isolation of a coagulase-negative staphylococcus from a catheter, whether it was from one or all lumens, to me, is good evidence that the catheter is colonized. Whether the catheter has resulted in or is the victim of a bacteremia with that organism, I think, for coagulase-negative staphylococci depends on corroboration.

It doesn't mean that the colonization of the catheter is not important or that it is not colonized. But I don't know how one can say that the patient has bacteremia, escaped bacteremia, if you will, with coagulase-negative staphylococcus without documenting it with a peripheral blood culture given the affinity of this organism for the plastic.

I don't think that is true for other organisms. If one got a Pseudomonas auruginosa out of a catheter, regardless of lumen, whether or not one, in that patient,

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had a corroborating peripheral venepuncture, I think one can accept that.

It would be nice if you got it out of the peripheral blood culture, but I don't think it can be discounted because it is not the sort of thing that we see with contaminants. Contaminants, as everyone here knows, are a real issue and they are a common issue and, in most laboratories, nowadays, account for at least as many positive blood cultures as all other organisms put together.

DR. CRAIG: You have gotten a lot of comments on blood cultures, at least. You may want to change that.

The other aspects that you had were new, different analyses. I think, Barth, you mentioned some. Do you just want to review those again that you had suggested, or don't you remember?

DR. RELLER: I remember perfectly. I just thought I've said enough.

DR. CRAIG: Just to summarize is because I am not sure I can.

DR. RELLER: The issues that clinicians caring for these patients faced each day and the decisions made, I believe, are based on persistence of fever and neutropenia, and that assessments related to the duration of those, as Dr. Soper has mentioned, possible objective ways of

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assessing or counting the days of temperature, would be, to me, important assessment points that would be useful.

They are, of course, correlated with the analysis, No. 2, duration before modification required because most of the modifications that come about in terms of added antibiotics have to do with persistent fever in the presence of neutropenia in these patients.

So they are related, but it is ways of measuring things that could compare the study drug with the comparator. For example, if I had a new compound that, in the presence of neutropenia in a patient who was febrile, could either get the fever to go away sooner or extend the days and the two would be related, of course, to when one had to intervene with another drug--it may be an antifungal agent--and, at the end of the day or the month or the return of granulocytes, there was also improved survival.

I think, simply living, is an important endpoint. It may not be a precise one but it is an important one, nonetheless.

DR. HENRY: It is one of our more easily measurable.

DR. RELLER: Seriously. If you had an agent that extended the time for you to intervention and bought more time, that would be an important consideration--bought time

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to modification. Ultimately, it would probably be associated with greater survival because not all of these people are going to survive their neutropenic episode or episodes.

So I think it is a matter of trying to make the assessment points match up with those objective markers that clinicians are currently using to decide intervention or modification of points, and that there really isn't a test-of-cure in these patients in whom you buy time, but there is not an entity that one can, for sure, have an objective way of knowing that you have eradicated it.

So it is measuring time and it is measuring forestalling interventions as opposed to measuring an entity that one has eradicated.

DR. CRAIG: But, would you want to have it relatively standardized as to how long the people would continue the drug in relationship to the neutropenia? You could give the drug for a short period of time and then stop, even while they are still neutropenic, or you could continue it until they are neutropenia resolves.

The latter would probably, if it works as a prophylactic agent as well, potentially look better than the first drug because, when you stop the therapy, you then open the patient up to getting another antibiotic.

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DR. RELLER: Arthur's comments here--I don't think these drugs are used for finite periods of time. They are not used in a three-day course or a five-day course. There may be drugs that come along that are effective used that way, but that is, in reality, now how the drugs are used.

They are used until something happens.

DR. CRAIG: By that, I mean, would be continuing it until neutropenia resolves.

DR. BROWN: My inclination would be continue until neutropenia resolves, would be the most common approach, I think, used by most people.

DR. RELLER: Right.

DR. BROWN: We all know there are lower-risk patients and subsets of subsets that we have begun to dissect out because of the pressures on us, and appropriate pressures, in managed care and so forth to find out which patients might not truly need to do this.

But the majority of patients, the majority of patients, really, should continue on antibiotics until their neutrophils resolve. That needs a definition, too, by the way. Usually, that is when it is crossing the 500 mark on the way back up.

DR. RELLER: If that is the commonest reality, then it is a matter of how many days does one agent or the

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other go--

DR. BROWN: Exactly.

DR. RELLER: --before one has to modify. Usually, the modifications are based on persistent temperature or some other clinical parameter. But, for the patients whose white cells are not coming back for a long time are the patients that one has the most rigorous test.

If one had an agent that forestalled modification longer than another agent, over the long haul, I would think this is the drug that people would want to use.

DR. CRAIG: But wouldn't you have to divide the number of days, as I say, by the total number of neutropenic days because there may be variation--

DR. RELLER: Exactly. That is the sort of analyses that I was trying to get at because it is consonant with practice. If we have a group-A streptococcal pharyngitis, we have got something that we can measure and endpoint on because it is also consonant with what people are trying to measure for the clinical entity.

I am just trying--rather than arbitrary durations and time points of getting the ratios and the proportion of days and so on to match up with the things that people are following and making decisions on clinically.

DR. BROWN: I would just like to throw something

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in here. I don't know why it didn't occur to me earlier, and it probably has occurred to all of you so it will be nothing new, if we were sitting here in 1970 and having this discussion, survival would be a very clear endpoint measurement, not that it is unclear now.

But we would be talking about regimen A versus regimen B and there would be lots of deaths and so forth and so on. We have the full expectation that 90 percent people with fever and neutropenia survive right now. I don't think there is any question about that. We have come a long way. We know what we are supposed to do.

It is because we do it quickly, effectively, and so forth. But we will have to have a survival--we have to follow survival to make sure that regimen A and regimen B don't have differences in survival. But the expectation is that they will all be in the 90 percent range.

So the differences we are looking at now are the things that Barth is talking about, that everyone else is talking about, indeed, is the time of defervescence different, is the time of--you might even talk about length of staying in the hospital, time until you switched, until oral antibiotics, if we are going to use an outpatient approach to things in the future and so forth.

These are going to be the shorter-term

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measurements and we should be looking at all of these as other forms of analyses, subset analyses, and so forth, along the way. But we can't, as Dr. Murphy said, discard the survival thing even though we expect everyone, or we hope everyone, is going to have this high survival.

I don't know whether I am saying anything new. I'm probably not. It is just that it occurred to me, as we were talking about dissecting out these little parts here, the little parts may well be the differences in the quality-of-life issue as well as in the efficacy kinds of things that are most important now, as we have become very successful at this process.

DR. CRAIG: What we have tended to do is look at those, but we tended to do them more as percentages in terms of patients instead of trying to use some other form of measurement like number of days, fever indexes, things like that, which give a little bit more quantity to it but also need to be validated, that they are appropriate endpoints and that they cannot be affected by other things that are unrelated to the drug therapy.

DR. MURPHY: Basically, I think what you have said is that, as we have improved, we are able to refine what we are able to look at, not just survival. Survival is important because, as I said before, it may tell us other

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things. We assume these drugs are equally efficacious and have other things that we do that we need to also look at.

But this discussion has been really very good. We really appreciate it.

DR. CRAIG: Anything else that anybody wants to bring up?

DR. ALTAIE: It could be a bit late at this point. I was trying to chime in as far as the blood cultures were concerned, but I am going to get it in anyway. Dr. Henry was concerned about the volume of the blood for detection of the organisms in the bloodstream.

To credit the industry that had worked very hard to develop techniques and media and detection methods that can work with lower volume of the blood, I would urge not to sacrifice the peripheral blood for getting more volume because then we have a problem with distinguishing and interpreting coagulase-negative staph.

So, I think concern about the volume was appropriate probably twenty years ago, but, since then, the sophistication in the blood-culture media and detection method has alleviated some of that volume need.

DR. HENRY: Let me make just one last comment. I guess I just wanted to clarify that. As far as a study is concerned, I think that a peripheral blood culture is

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warranted as well as blood cultures through the lumens.

We were sort of getting off-track talking about day-to-day practice and once a patient is in the hospital with fever and neutropenia, do you always have to sample peripheral blood. My point there was no, but I think for purposes of the study, you obviously have to, especially with this idea of trying to sort out those that are line-associated bacteremias.

DR. GOLDBERGER: John, could you put up slide 22. While John is doing that, just a comment about using as an endpoint the time to modification of therapy. We should keep in mind that has the potential to be a composite endpoint; that is, on one hand, a difference in efficacy and, on the other hand, a difference in toxicity.

On occasion, those two may move in different directions--I'm sorry; slide 12--we need to be aware that combining the two of them together may not be ideal because, in fact, they are going in opposite directions.

The other comments was everyone has been talking about our expectation that mortality will be up in the 90's et cetera, and we ought to be looking at the other endpoints.

[Slide.]

If you take a look at this slide here, and we look

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at outcome 3, which is mortality, regimen C and regimen A, I would submit, are, from a point of view of survival, quite different from one another. The absolute difference is 5Êpercent. If you were just to crudely estimate the relative risk, the relative risk of death would be 2 for regimen A versus C.

If you were to produce a confidence interval around that, it would be up at the high end, to 3 or 4. I think that, although we say that we are expecting it to be in the '90's, we need to be careful that, when we are talking about a relatively common phenomenon, several points difference in survival still represents a noticeable difference in the impact on patient care. So we do need to be careful about that.

DR. DOERR: Mary Beth Doerr, Rhone-Poulenc Rohrer. We have a compound that we think will benefit patients with fever and neutropenia. We are very grateful that the FDA has put together these guidances.

However, our compound doesn't fit easily into the guidance in that our compound is directed against Gram-positives. In 1997, the IDSA published guidelines which would limit the use of compounds directed against Gram-positives to modification therapy except in specific circumstances.

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So we have a little bit of a dilemma in that we are not 100 percent sure how to take these guidances and apply them to a modification therapy design. So that is one question.

The second question is how do we power our study. You have mentioned three different populations. If we are looking at empiric therapy, would it be more appropriate to power the study on the modified intent-to-treat or is it more appropriate, as Dr. Brown has suggested, the microbiologically defined patient is the one that we want to make sure we can understand the outcome, is it more appropriate, then, to power the study on that criteria.

DR. CRAIG: Do you want to consult with them?

DR. MURPHY: I was going to say that I think that we are not here to do that today, to develop specific drug programs. I think that there is no way these guidances will ever fit all drug programs. Even it were more generalizable, obviously, each drug is going to have its own profile for efficacy, toxicity.

One needs to think of these, if you will, a template upon which you fit your specific needs. I do think that Dr. Lin would like to comment on the power issue. I think that might be wise. She is raising her hand. I am not sure. We will find out.

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DR. LIN: My comment is a general comment. I think there is power for both.

DR. CRAIG: And, again, I would just comment that things have changed a lot since the FDA guidelines were written and there are, clearly, a lot more Gram-positive infections than were present then and also with more resistant organisms.

So I think, clearly, it is difficult to use those guidelines exclusively. Talking to the agency is clearly the thing to do.

DR. FOX: Barry Fox from Bristol Myers. I would like to just readdress the issue of inclusion criteria with respect to the absolute neutrophil count of 500 and the now 24 hours requirement for onset to less than 500.

Dr. Brown told us that even at his institution they used 1000 as the criterion. My concern is, by going to 500 within this 24-hour period, now, it just seems to me that we are going to have patients that come in with an absolute neutrophil count of, say, 1600 or so. They get started on empiric therapy because it is anticipated that their counts will be less.

The next day, their count will be 600 or 650. It seems to me that we are going to lose 25 or 30 percent of patients by the inclusion criteria by having this 24 hours.

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What my suggestion potentially would be is, if the count is greater than 1000, have it be between 500 and 1000 within 24 hours and then less than 500 within the 48-hour period.

Any comments regarding this?

DR. BROWN: Yes. I would have a comment about that. I don't think anyone whose count is 1600 should be started on antibiotic therapy, anticipated or not. 1600 os not neutropenic by any measure of any kind of study or any clinical parameter used by clinicians in this country.

I think that is stretching things out of the boundaries of what I have thought, and I am open to thoughts of other people. But as I recall the way this is written, it was supposed to be there was disagreement among people who wrote guidelines of whether it was 500 or 1000.

I don't remember anyone who was saying that, well, if you are 1500 or 2000 or 2500--you could go up and up and up and say, yes, it is anticipated that I gave thermotherapy today and ten days later, this person is going to be under 500. So I think that is stretching the point a bit.

I was trying to get, in saying this and throwing it out, to get some uniformity here and some homogeneity in terms of making sure the population that we are looking at here is more of the same and not spread out and so forth. We are talking more about the same kind of apples, so to

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speak, not just apples and pears but the same kind of apples, and so forth.

So I would say that it is supposed to be between 500 and 1000--you can measure it on the day that the patient is febrile and it is 500 and 1000. But if it is anticipated to drop less than 500 within 24 hours, that is an inclusion and, indeed, after the study, the patient is entered and, indeed, it turns out to be they are, then they would be counted. If they didn't drop to that level, they wouldn't be counted.

DR. CRAIG: I think our indications of what we have tried to say is that we are not writing guidelines here for the use of the drug in clinical practice. What we are trying to do is look at it for safety and efficacy and so we have tended to, oftentimes, tighten up on the inclusion criteria so that we are clearing looking at fever and neutropenia to insure that the population is what they are supposed to be so we can see if the drug really works in that population.

DR. FOX: Thanks.

DR. RELLER: Art, could you comment on patients with fever and neutropenia. What we heard was the white count is coming down and you stuck with 24 hours until it plummets below 500. Theoretically, what would happen is you

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would plummet below 500 before the fever came about.

Are we anticipating the fever as well as the neutropenia with these early interventions or should a patient have--I think we need to emphasize that it is fever and neutropenia.

DR. BROWN: Yes; it is.

DR. RELLER: Because the creep goes such that patients who are afebrile, who have a normal white count, are started on antibiotics in anticipation that they are going to have neutropenia and the anticipation that they are going to have fever. One gets so much anticipation that it ends up being everybody who has the entity; that is, the AML gets temperature and anticipation that somebody they are going to get chemotherapy and be neutropenic.

DR. BROWN: Both.

DR. RELLER: It is slippery.

DR. BROWN: It is both. It seems to me that, at time 0, when the patient--presumably, a patient calls up and says, I have fever, because they were told that when their temperature is about X, they are to call in.

They come into bed holding, emergency room, whatever, and, indeed, they still have fever. So there are your two measurements above 38 within--did we decide how many hours?

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DR. ROSS: Twelve.

DR. BROWN: A certain period of time.

DR. CRAIG: So it is 24, isn't it?

DR. BROWN: Their white count is measured at that point and the neutrophil count, indeed, let's say, is between 500 and 1000 but it is anticipated that it is going to drop below 500 within 24 hours of that entry time. All the fever for that time would count.

I don't think it can be done for anticipated fever. I agree with you.

DR. RELLER: The reason I emphasize this is because, it seems to me, that the issue of--that it reinforces sticking with the 24 hours because the fever, in these patients, we are assuming is related to the neutropenia. If they have fever that is not associated with the neutropenia, then that is not the body of patients that is being studied in these trials so that it would not be an issue of being below 500 within 24 hours if it is patients with fever and neutropenia that are being studied as opposed to patients who have an underlying disease that are febrile who then get chemotherapy.

DR. CRAIG: I guess the only the only question I would ask is we did have the open public hearing. Did the person from Nexstar feel that--did you want to finish up

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what you had said or are you done?

DR. SANDHAUS: I think the questions have been answered.

DR. CRAIG: Okay. Thank you very much.

I would, then, say we are adjourned.

DR. CHIKAMI: I just wanted to make a couple of comments as we have wrapped up this two-and-a-half days of meeting. First of all, I would like to thank the committee members and our consultants and guests for really reviewing lots of material in a relatively short period of time, particularly for the discussions that have gone on.

They have been very helpful and sort of right on target in terms of how we will use the discussions to modify these draft documents over the next 90-day comment period and include comment from the public.

I would also like to thank the audience who stuck it out for these two-and-a-half days and for questions and input because we also feel that is important as we modify these documents.

Most importantly, I would like to acknowledge the staff within ODE 4 and the divisions for all of the hard work that they have put in in producing these documents over the past couple of months and the time that has been put in in preparation for the presentations.

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I think the presentations have been of very high quality and have really been right on target in terms of identifying the issues that needed to be discussed for each of these documents.

Then, most of all, I would like to acknowledge Renata Albrecht who has really been the coordinator for this entire effort and has really been sort of the driving force in getting all this work done.

So thank you very much.

DR. MURPHY: I did have one last comment for the committee. When we told people we were going to review eighteen guidances issued by the FDA, eyes would glaze over, people would become limp. I would like to say to both the Division and the Advisory Committee, and the audience, you have taken these boring, dull guidances and have not only made the discussion simply informative; it has been really stimulating, reinvigorating and, Barth, it makes me realize my fellowship was some of the best days of my life in your microlab.

Thank you all, and we will see you again.

DR. CRAIG: We are adjourned.

[Whereupon, at 11:40 a.m., the meeting was adjourned.]

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